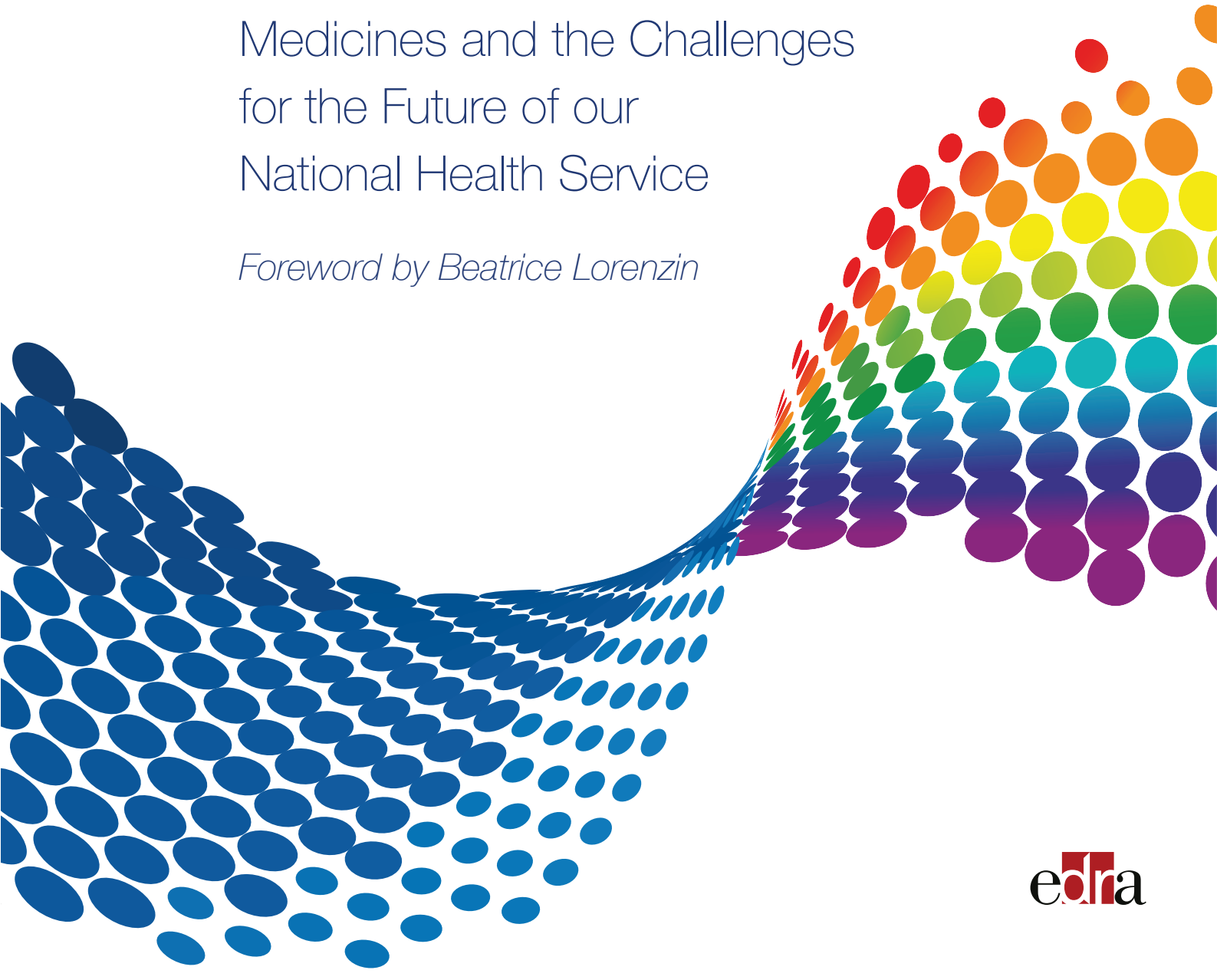
Agenzia Italiana del Farmaco
AIFA

Luca Pani

Sustainable Innovation

Medicines and the Challenges for the Future of our National Health Service

Foreword by Beatrice Lorenzin



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Luca Pani

SUSTAINABLE INNOVATION

Medicines and the Challenges for the Future of our National Health Service

By the Press and Communications Department of Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA)

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To my wife Anna Maria, metaphorical palindrome of my life, who has endured me beyond any reasonable doubt.

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Foreword

Beatrice Lorenzin

As this book goes to press, the US Food and Drug Administration (FDA) has started to evaluate the first New Drug Application for a digital medicine. The application concerns a pharmaceutical product for the treatment of mental disorders, which combines a chemical molecule and an ingestible radio frequency sensor, smaller in size than a grain of sand. Once ingested, the sensor is activated by the acidic pH in the stomach, and transmits information to an external receiver placed on the patient's body, and from there to a smartphone and the cloud. This will allow physicians to be constantly informed on treatment compliance and changes in physiopathological parameters.

The researchers who told me about these wonders, considered visionary until yesterday, describe these brilliant early results as the latest evolution of the *Pharma* species. Just like the author of this book, they now see the future heading directly towards the decline of traditional medicine, and biological and clinical sciences transformed into information-based multimedia disciplines.

They cannot be far from the truth, considering that some pharmaceutical companies (the so-called 'Big Pharma') have thought of facing this new challenge with the support of partnerships with non-traditional players such as IBM, Google and Apple.

I have heard of Watson, a technology platform developed by IBM that analyses unstructured data, approximately 80% of all existing data, and puts them in relation to each other. Clearly, it is no longer only a computer but rather a true cognitive system that uses predictive models from unrelated skills. Watson matches huge amounts of molecular and clinical data on a 24/7 basis, trying to simulate possible side effects or to identify with a high degree of accuracy the mechanisms of action of old or new active substances on biological targets (*biomarkers*), and then design increasingly targeted, fast and therefore cost-effective clinical trials.

In order to develop medical applications, Watson was "trained" by the New York *Memorial Sloan Kettering Cancer Center*, first in oncology and more recently in the search for the most suitable ongoing clinical trials for any patient with any neoplastic disease, anywhere in the world.

For quite some time now, Google has been more than "just" a search engine. Along with Facebook, it is probably powered by the most sophisticated predictive mathematical algorithms that have ever been developed, and that are now used in medicine. A few months ago, Google entered into an alliance with a pharmaceutical company to develop better ways than the existing ones to collect, analyse and understand the existing databases on type 1 and type 2 diabetes. These new applications include portable sensors ranging from smartphones to smartwatches, as in the case of Apple's ResearchKit.

As we take in all this, we cannot help thinking how urgent it is to equip our National Health Service, so as to safeguard its impressive wealth of expertise, value, and above all solidarity. New discoveries should improve the quality of care for everyone. Solidarity is the principle to which we should link any development, any future. In order to achieve this and to preserve what the NHS is to all Italians, we must be able to anticipate the challenges we will need to face in the coming years. The Copernican revolution of medicine will not happen over a decade, but within the next 12-24 months, and it will not be just the result of a "technological shock" but rather of a series of paradigmatic leaps that are already leading towards a new way of building the patient-doctor relationship. This book helps us understand all this, and perhaps more.

Beatrice Lorenzin
Minister of Health

Acknowledgements

Luca Pani

I had the idea to write this book in December 2011, shortly after being appointed interim Director General of Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA). It soon became clear, with a good deal of what could be described as visionary awareness, that the regulatory world (and others as well) would be facing some formidable, but at the same time extraordinarily stimulating scenarios in trying to solve one of the great challenges of the modern age: the future of sustainable innovation.

A lifetime dedicated to clinical practice, research, development and, more recently, to the evaluation of pharmacologically active products provided the insight to see how, in this area, nothing would ever be the same as it had been. The world of pharmaceutical care, as we had known and managed it, would be forever revolutionised by new, increasingly personalised treatment options, even designed for individual patients, in some cases at extremely high costs. To manage such a change, regulatory agencies like ours would need to adjust with new procedures and increasingly complex organisations, while continuing to provide the healthcare that patients were accustomed to and which, as we have seen, they would continue to demand. A momentous challenge that AIFA anticipated and accepted well in advance, especially at international level, and which has been the subject of in-depth coverage constantly presented to the public through the institutional website and social networks. The significance of the topics covered, the debates taking place worldwide, the comparison between different experiences with the common goal of ensuring the sustainability of innovation and bringing science to the fore of the regulatory system, are the basis on which this book was conceived as a tool for reflection for citizens, healthcare professionals and institutions.

I would like to thank all those without whose assistance I would not have been able to complete this project.

Those who decided to follow me in this direct communication approach and who wrote for the Agency's website with commitment and dedication. A very special thanks to the young people (some of them are very young indeed!) of the Press and Communications Department, who always met the requests I would make at all hours for an article to translate, an editorial to adapt, an idea to pursue and develop, which you can find in every chapter of this book. I am also personally grateful to the executives, officers and technical-scientific as well as ad-

ministrative staff of all AIFA departments for the hard work and dedication that underlie the Agency's everyday activities, and that are the very substance of the stories dealt with in this project.
Undoubtedly, all of us here at AIFA have a great opportunity to improve people's lives, but we also have heavy responsibilities. So it is only fair to mention the motives that make us honour oaths that go back thousands of years and that give us the strength to try to do more and better.

I am reading proofs while flying to the United States for a few days on a trip to see my wife and my two American children, whom I have been able to see so little of over the last four years and to whom I dedicate this umpteenth editorial effort, because I owe them just as much humble gratitude. Just before boarding, I received a message on Facebook that said: "I have been following you on Twitter for a long time. I had a chance to meet you at an EpaC Meeting on new HCV medicines; I am aware that since you have been at the head of AIFA, many things have changed for me as well. Before receiving the compassionate treatment with sofosbuvir + daclatasvir I was a candidate for liver transplant, but given the results this is no longer the case. It was a success, both for me and for you. Keep up the good work."

I would like to extend this to everyone involved.

Luca Pani
Director General of Italian Medicines Agency
(Agenzia Italiana del Farmaco – AIFA)

Introduction

"I maintain there is much more wonder in science than in pseudoscience. And in addition, to whatever measure this term has any meaning, science has the additional virtue, and it is not an inconsiderable one, of being true."

Carl Sagan

Along with other public institutions, Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA) plays a major role for the protection of health in our country. Its function is to ensure that medicinal products marketed in Italy are effective, safe and compliant with the quality requirements imposed by current legislation; that pharmaceutical research be encouraged and focused mainly on unmet needs and innovative therapies, and that all this be carried out in compliance with State budget constraints.

The Agency is also committed to promoting a culture of medicines, which means disseminating among health professionals and the general population scientifically validated information on the methods, times and advisability of taking a medicine: in other words, ensuring an appropriate use of medications and patients' compliance with treatments while monitoring and reducing side effects as far as possible.

Achieving these goals requires competence, willingness to dialogue, transparency and independence from anyone – sometimes, paradoxically, even from itself. Moreover, the ability to communicate knowledge is increasingly important so as not to leave the field open to disinformation, partisan interests and bad faith, which lurk everywhere and have the potential to generate serious consequences for people's health.

Aware of this, in recent years AIFA has intensified its information and communication activities on topical regulatory and scientific issues, arousing the attention and interest of both industry stakeholders and the public at large and contributing to the debate on the new scenario that is emerging globally in the world of pharmaceuticals and of healthcare in general.

In this book, the Agency collects and systematises by theme areas a small part of the material posted on the institutional portal in the past two years, with additions and updates where necessary, to give readers a dynamic view of the topics covered.

"I maintain that there is much more wonder in science than in pseudoscience" said Carl Sagan, one of the most distinguished astronomers, astrophysicists and astrochemists of the 20th century. That "thought-provoking sense of wonder", which is innate in man and fills children with curiosity and thirst for knowledge, loses its momentum for lack of encouragement as we approach adulthood. When science withdraws, giving up its enchantment potential, that opening that is no longer protected is taken over by the germ of pseudo-science, which penetrates it and proliferates.

Recent news reports have provided a variety of examples of denial of science and delegitimization of the set of rules underpinning the credibility of the international scientific community. Those rules have allowed man to make a great many breakthroughs in several fields of knowledge and to learn about the world and himself, to take care of himself and others, to cure diseases and prevent them.

In view of the public's thirst for knowledge and of the large amount of more or less reliable and verified sources of information (or pseudo-information) available at a click, it is even more necessary for healthcare, academic and educational institutions to ensure a qualified presence in the globalized and complex world of scientific communication. We need to promote a more mature awareness in citizens, enabling them to distinguish good from bad information and not to be led astray by charlatans and conspiracy theories.

This is how AIFA intends to continue to contribute to the debate on issues which, directly or indirectly, have great relevance to public health and the future of our National Health Service (NHS).

1. New drug policies in a changing world

Considerations on the universality and solidarity of the National Health Service and its prospects on the one hand, and the repeatedly proposed cuts on the other, can only lead us to emphasise the need for a comprehensive review of drug policies. Such a review should be carried out in light of a number of factors, clearly identified in the programmatic analysis recently published by the European Commission, which have and will have a major impact on health, the right to medical care, and global economic sustainability.

1.1 Right to treatment for all: a challenge for the entire National Health Service

Provide all citizens, regardless of socio-economic conditions, with primary healthcare and essential medicines is a non-negotiable prerogative of our National Health Service (NHS). Even countries that have always had a different public approach to healthcare, like the United States, have launched discussions or reforms designed to extend basic medical coverage as much as possible, to put a stop to inequalities between those who can afford health insurance and others who do not have the same opportunity.

Our NHS is still a flagship of public health, and it is what guarantees that everyone, even the poor, can access primary healthcare through the dispensing of essential medicines for major illnesses. Three quarters of Italy's total pharmaceutical expenditure are borne by the NHS; this is a source of pride, but it is also a commitment for those who are responsible for decisions that have a direct and immediate impact on the health of all. Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA), whose role is to protect the health and economic sustainability of the entire Italian pharmaceutical system, now faces the challenge posed by the new drugs – particularly the truly innovative ones – that will mainly affect hospital spending. On another front, we need to address the final patent expiry period of the so-called 'blockbuster', which in recent years has allowed the control of local pharmaceutical expenditure by promoting the use of equivalent medicines.

New ways will have to be identified to provide people with the care they need; to achieve this, we will need globally shared strategies. Globalisation has affected all the stages of a medicine's life cycle, from clinical trials to the production and marketing of raw materials, from counterfeiting to pharmacovigilance, through the management of scientific information and sensitive or financially significant data. Only a comprehensive view and borderless cooperation can help us control this complex machine.

But we need to dare to make specific choices: for example, to optimise investments in Research and Development and to recognize, promote and reward true therapeutic innovation. Here again, AIFA has had the courage to indicate a path that has already received recognition and approval in Europe and worldwide, through an algorithm dedicated to innovation.

Also of paramount importance is cooperation with health professionals who work in the individual Regions of Italy, to whom the Agency provides valuable support for prescription appropriateness, e.g. the new Monitoring Registers, the Notes, the Formulary and the treatment decision pathways posted on the institutional portal[1].

One of the priorities is authoritative, independent information able to transmit trust and awareness and to provide people with the tools they need to orient themselves in the flow

[1] http://www.agenziafarmaco.gov.it/it/content/terapie-spersonalizzate-e-il-futuro-della-medicina.

of often partial, unreliable and distorted information, disseminated especially in the web on issues related to health and healthcare. We often see cases where ideas that have not been scientifically validated are transformed by "popular will" into data worthy of scientific consideration, or even of claims for reimbursement. The emotional wave that has recently accompanied the stories of children with very serious diseases and the distress of their families, willing to do anything to kindle the slightest hope, brings to mind similar situations that occurred in the past, when propaganda for persuasive purposes, combined with inadequate scientific and political debate, used patients' understandable and legitimate desperation and suffering to overshadow and hinder the reasons of science and medicine. More often than not, however, there was no evidence whatsoever in support of the efficacy and safety of these alleged life-saving drugs. In all these cases, it is the health authorities, and particularly the regulatory bodies, who are responsible for the delicate task of making decisions based on rigorous scientific method, going beyond subjective perspectives and emotional pressures. This is necessary, in the first place, out of respect due to patients and their families, who have the right to well-founded hope and cannot be sacrificed on the altar of other interests, which thwart real achievements and take away energy and resources that should be employed virtuously to ensure healthcare for all.

In an editorial[2] published in November 2014 in the *New England Journal of Medicine,* Michael Stillman and Monalisa Tailor, two physicians of the Department of Medicine at the University of Louisville, KY, denounced how terribly and tragically inhuman it is that tens of thousands of Americans die every year for lack of health insurance, and questioned the American welfare system and their own responsibilities as health professionals.

"First," they wrote, "we can honor our fundamental professional duty to help. Second, we can familiarize ourselves with legislative details and educate our patients about proposed healthcare reforms. Finally, we can pressure our professional organisations to demand health care for all."

Being deprived of health care means not being able to afford early diagnoses and expensive procedures and treatments. American physicians are well aware of this, as they come across scores of doomed men and women – patients who, though employed, have no health insurance and must give up even the right to hope. Many doctors do not accept being powerless, and do all they can to stem this problem or encourage a change in culture.

The right to health is one of the fundamental principles of our Constitution (article 32): it is a right for citizen and a duty for the community, closely linked to another pillar, that of equality between citizens. This seemingly simple concept is actually very complex and far from being a given in its day-to-day recognition and application. It means providing the entire

[2] http://www.nejm.org/doi/full/10.1056/NEJMp1312793.

population residing in Italy with the education and information tools required to be aware of their health, of avoidable lifestyle-related risks, of the value of prevention and early detection of diseases; ensuring environmental, workplace and social conditions that will allow everyone to follow a correct lifestyle and have timely access to diagnosis and treatment, and an efficient healthcare network that supports patients in the different stages of their disease.

A challenge that requires a shared commitment by legislators, health institutions, healthcare professionals and citizens. A challenge we need to address every day with a strong sense of responsibility.

1.2 Healthcare cuts: reckoning with health

Amazement and disbelief: this is the reaction we encounter most frequently when we tell our foreign colleagues that the Italian National Health Service (NHS) bears a share well in excess of 75% of the total pharmaceutical spending, and is the only one still able to guarantee basic care to all citizens (and even to illegal immigrants).

So far, one cannot help thinking. The buzzword in vogue in the public debate now is "cuts" or, in the politically correct version, "reduction in healthcare spending". In hectic days full of charts, simulations, economic models brought to the extreme consequences, Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA) has also discussed, based on hard figures, the so-called "cuts" (across-the-board or otherwise) to pharmaceutical expenditure. In particular, we asked ourselves what would be the effects of a hypothetical reduction in the budget for pharmaceutical care and spending coverage procedures if the upper limits were exceeded. We assumed a value of approximately 1.1 billion euros per year for three years of the total National Health Fund (FSN), which we then used as a basis to calculate the amounts required to finance the pharmaceutical, local and hospital expenditure.

If these assumptions were true, in the 2015-2017 period the funding of pharmaceutical care would undergo a reduction of 215 million euros (about 70 million a year): this may seem a quite modest amount, were it not for the fact that several important products will be in the process of being registered in the same period. Additionally, the proposed measure would affect to a considerable extent hospital pharmaceutical expenditure, which is already significantly above the 3.5% limit, while for local spending the effect could perhaps be less pronounced, since this cost item is "apparently under control"; however, the treatments that are becoming available (and those that will become available over the coming years) may change this scenario and generate incremental costs for the NHS that will certainly exceed the currently estimated surplus, also with respect to the limits applicable to local expenditure, for example with the reimbursability of treatments against hepatitis C. All this should be part of a general framework where the costs of public healthcare facilities, including hospitals, grow at an average annual rate of 457 million euros, while the expense borne by citizens simultaneously increases in parallel.

Clearly, such a scenario would make it increasingly difficult to guarantee to all citizens free access to new medicines, which in most cases would be added to hospital expenditure. For the latter component, in the next three years the deficit over the set limit of 3.5% may amount to several billion euro, of which approximately 2 in 2015 alone.

If all these figures were not enough, the analysis is made even more complex (as noted publicly by Health Minister Beatrice Lorenzin on several occasions) by the fact that we are on the threshold of a revolution in the pharmaceutical industry. A series of innovations, produced

in laboratories and research centres in the last decade, are reaching the global and the European market, all with centralised procedure. These are heterogeneous products, some with high therapeutic potential and equally high costs, able to disrupt well-established calculations and reasonings, and above all, the models used so far.

Other molecules, perhaps even more advanced and sophisticated, will be developed in the near future. In addition to other therapies for hepatitis C, applications for registration are being filed for monoclonal antibodies to try to fight Alzheimer's disease and dementia in general, cancers (e.g. breast, lung, colorectal, pancreas, kidney and melanoma), LDL cholesterol, asthma and some bacterial toxins. There will be new antiretroviral drugs, with an estimated financial impact for the NHS from several tens to several hundreds of millions of euros over the next two to three years. Our fund for conceptually (as well as financially) outstanding innovation, recently financed with 500 million euros of dedicated funds, might not be enough and will have to be adjusted to avoid destabilizing the entire Italian pharmaceutical system.

Will we be able to reimburse all of these new drugs? Will we be able to ensure access to all patients who need them, preserving the unique solidarity and universality of our public healthcare? Will we be able, now and in the next few years, to reward pharmaceutical innovation and support investments in Research and development that promise new milestones in the treatment of serious and rare diseases? Can we answer these questions while discussing cuts and reductions, which would further strain already badly stretched budgets?

Meanwhile, another world has permanently come to an end, namely, that of highly profitable blockbuster pharmaceuticals, generating over 1 billion dollars a year, with a broad spectrum of use and relatively low costs per package when compared with the costs of the products about to be introduced. The time when the industry picked "fruit from the lower branches" is gone. Today we study and develop biotech drugs, "personalised" on precision genotypes that should act on selective targets.

We are aware that the research and development of this type of molecules involves significant time and cost, but in the absence of new modes of interaction between regulators, payers, health professionals and companies, such strategies will lead the system to financial collapse.

The mechanisms that so far have allowed us to control the pharmaceutical expenditure, ensuring access to essential care, will no longer be sufficient: all the "old" molecules have lost patent coverage or will lose it over the next two to three years (around 2017), and the savings generated from the promotion of equivalent medicines will no longer occur, while despite major initiatives also supported by AIFA, the use of biosimilars does not seem to produce the desired savings.

For the new world, we will need new paradigms and new strategies. We must have the courage to state clearly that the proportion of the National Health Fund (FSN) that will positively be dedicated to hospital medications and most likely to those for local use will no longer

be adequate to ensure patients' access to products that have real therapeutic innovation potential. It would be simplistic to think that a few measures, albeit specific, may be able to help us journey safely into a future full of unknowns. The cornerstone could be represented by a change at European level, inviting Member States to make their drug pricing and reimbursement procedures as consistent as possible and experiencing, through the European Medicines Agency (EMA), with new marketing authorisation methods.
The Continent's entire regulatory system is questioning and attempting to redefine the underlying rules, in the awareness that the process will have to be undertaken again whenever a series of disruptive innovations perturbs the balance that has been laboriously reached. Italy should prepare itself, proving its ability to meet the demands of pharmaceutical innovation and to provide adequate responses to population's legitimate demand for healthcare.

1.3 Pharmaceutical challenges in a hyper-globalized world

As we have seen, drug policies are one of the key challenges for today's public decision makers. These choices influence not only the availability of safer and more effective therapies, and therefore the possibility of improving people's health and quality of life, but also the sustainability of financial systems, given the incidence of pharmaceutical spending on overall health expenditure and of the latter on public budgets.
Not coincidentally, the European Commission has recently dedicated a programmatic analysis ("Pharmaceutical industry: a strategic sector for the European economy")[3], to the pharmaceutical sector as a starting point for defining a strategic agenda for facing the priorities and upcoming challenges.

1.3.a The current pharmaceutical industry

The global market is expected to reach nearly 1.4 trillion dollars by 2020 (it stood at "only" 1 trillion in 2015), with a growth of approximately 80 billion dollars per year. Not even the global economic crisis seems to have been able to prevent the long-term expansion of pharmaceutical expenditure, considering factors such as the ageing population (the number of over 65-year-olds is expected to increase from 92 million in 2013 to 148 million in 2060), the growing prevalence of chronic diseases (metabolic syndrome, diabetes and dementia), the appearance of new diseases and the re-emergence of those that were believed to have been eradicated (including some serious infectious conditions), climate change, antimicrobial resistance, and of course cancers. We need to come to grips with the new pharmacological treatments, often much more expensive, and with patients' right to timely access to safer and more effective drugs. Outstanding advances in our knowledge of the human genome, biotechnology and precision medicine are creating even more ambitious expectations in society and patients towards new and more effective pharmacological treatments. This scenario represents a new reality, for which the strategies of the past have become obsolete and frankly inadequate. Based on hard figures, the first step is to acknowledge the radical change that is affecting the world of medicines.

From research to market: usefulness of dialogue between companies, regulators and other entities

We always hear of how Research and Development (R&D) aimed at finding new molecules has become more complex, expensive and risky. R&D costs stand at approximately 1 billion euros for

[3] http://ec.europa.eu/DocsRoom/documents/7649/attachments/1/translations/en/renditions/native.

each new drug introduced in the market, while in 1975 they amounted to less than 150 million euros. How these figures are obtained is not known in detail, yet they are consistently reported by everyone involved. These efforts do not always produce successful outcomes, suggesting that perhaps the R&D model should be radically reformed. In fact, only 5 out of 5,000-10,000 potential medicines that are investigated reach the clinical trial phase. Only 1 of these receives a positive opinion for marketing authorisation by the regulatory agencies. Regulatory authorities and companies, as well as patients and prescribers must help to improve the overall efficiency of the system. We all have a responsibility to recognize, support and promote real innovation, facilitate the procedures to introduce new drugs in the market, intervene where economic interests could prevail on real health needs, even when these concern populations that are smaller, special, or not as "protected" by the public opinion.

The industry, in turn, should take the opportunity of interacting with the regulators from the start, so as to design better trials, speed up the development process and reduce the risk of failure. As demonstrated by recent data[4], the Scientific Advice provided by regulatory agencies is proving to be crucial to the success of applications for authorisation.

AIFA has developed a series of tools to support regulatory, clinical and administrative activities in order to obtain information useful for decision-making purposes. The Managed Entry Agreements, which the Agency introduced several years ago and which it supports with the new Monitoring Registers (ranking Italy among the world's leading countries in this area) allow new treatments to be made available to provide, while ensuring close monitoring of therapeutic benefits and of the efficacy to safety ratio in real life. Constant interaction between regulatory agencies and welfare systems also allows the adoption of an "in-progress" approach to the authorisation process, moving from a static concept of authorisation to the so-called "progressive authorisation". Adaptive licensing, or more accurately the progressive patient ac-

[4] http://www.agenziafarmaco.gov.it/it/content/agenzie-regolatorie-e-industria-l%E2%80%99importanza-di-un-dialogo-precoce.

cess scheme, which the EMA is experimenting with in several pilot projects, is a prospective authorisation process that begins with the early authorization of a medicinal product in a limited population of patients, and continues with a series of iterative phases where evidence is collected and the authorisation is adjusted so as to extend access to the drug to increasingly large patient populations.

In order to face the challenges represented by patients' access to innovation and the sustainability of the public health systems, we would need to accelerate and combine the Health Technology Assessment (HTA) and Scientific Advice procedures in the early stages of drug development, and review the risk-benefit and benefit-price-reimbursement ratio each time their efficacy and safety is (re)-assessed in real-life clinical practice.

AIFA is proceeding along this direction, given that the heart of Italy's strategy consists of the new Monitoring Registers, i.e. dynamic databases that collect certified and validated epidemiological data directly from clinical practice. The Registers provide valuable information on medicinal products' real efficacy and appropriateness of use, and aim to constitute the only sources of real-life regulatory evidence. The third large database through which drugs are re-assessed after their introduction in the market, in addition to the Registers and the HTA, is pharmacovigilance. The active role of pharmacovigilance has been emphasized by the new European regulations, which expand the scope of stakeholders, facilitate reporting, implement the European network and extend the concept itself of "adverse reactions". The lack of effectiveness of a drug, for example, should be considered to all effects as an adverse reaction, the reporting of which is extremely important to the entire system.

The European Commission's report highlights the need to harmonise drug policies, taking into account the interrelationships that are inevitable, in a unified world market, between the policies of the different EU and non-EU countries. Short-term considerations, often justified by budget considerations – points out the Commission – can lead to ad hoc national measures that have economic repercussions in other EU countries and beyond. One example is the External Reference Price (ERP) system, adopted by the majority of national authorities, which involves determining the price on the basis of those applied in some reference countries (or the lowest price). In light of the economic crisis, some countries have taken emergency measures that have led to a significant reduction in medicines reimbursement prices. Therefore, while on the one hand the ERP mechanism can provide useful benchmarks[5] for pricing negotiations between public authorities and companies, on the other hand the Commission points out that some stakeholders[6] complain that ERPs are applied without taking into account

[5] Index adopted by investment companies as benchmark to evaluate the return of a particular investment and present it to clients on a comparative basis. Source: www.treccani.it.

[6] All the parties, whether individuals or organisations, who are actively involved in an economic initiative (project, enterprise), whose interest is negatively or positively influenced by the result of the execution or performance of the initiative and whose action or reaction in turn affects the phases or the completion of a project or the fate of an organisation. Source: www.treccani.it.

each country's socio-economic characteristics, and in particular the fact that reference prices affected by some emergency measures can influence price levels in other member or non-member States. Today we know that price management in a national context also has implications in non-EU markets for our pharmaceutical industry, because non-European countries (particularly high-income emerging economies like Korea and Taiwan), make extensive use of ERP using European countries as benchmarks.

Intellectual property: from patents to trial data management

According to the Commission, regulations on intellectual property (IP) have specific significance, since the nature itself and the development of medicinal products makes companies highly dependent on their ability to adequately protect patents. For this reason, the European Union has felt the need to ensure a single European of intellectual property system[7] and other intellectual property protection tools that address the specificity of medicinal products, including Complementary Protection Certificates (CPC), intended to compensate, at least in part, any commercially significant losses for the time elapsed from patent filing to the actual marketing of a medicine.

The issue of the proprietary nature of preclinical and clinical data is very complex and debated. In this respect, AIFA has long expressed its position clearly and unequivocally[8]. The Italian Agency believes that the transparency of clinical data allows a fruitful sharing of information and knowledge; meets the legitimate transparency expectations of patients, who want to understand the risks and benefits of treatments they are or will be receiving, and represents an economic advantage for the companies themselves.

The world of clinical trials has changed, and those who fail to understand the importance of sharing information, controls and trial data will undoubtedly find it more difficult to maintain their market positions.

January 1, 2015 saw the entry into force of the new EMA policy on the publication of clinical reports that form the basis of the decision-making process on medicines; the policy will be applied to the clinical reports contained in all centralised applications for marketing authorisation. As has been pointed out by EMA itself, the new policy aims to provide a useful complementary tool for the implementation of the new EU Regulation on clinical trials, which will come into force no sooner than July 2016. EMA expects the new policy to increase confidence in its regulatory activities, as it will allow the general public to better understand the Agency's

[7] http://www.agenziafarmaco.gov.it/it/glossary/term/1434.

[8] http://www.agenziafarmaco.gov.it/it/content/pieno-sostegno-dell%E2%80%99aifa-alla-policy-di-trasparenza-dell%E2%80%99agenzia-europea.

decision-making process. Additionally, academics and researchers will be able to reassess data sets. The publication of clinical reports will also avoid the duplication of clinical studies, promoting innovation and encouraging the development of new drugs.

1.3.b New global competitors and the safeguard of quality

Hyper-globalization means new market opportunities, but it also means more competition, which in the pharmaceutical sector is no longer confined to traditional competitors like the United States or Japan. Several emerging countries, particularly in Asia, are looking at life sciences as future drivers of economic growth and are investing in biomedical innovation. The goal of these countries is twofold: on the one hand, to reduce dependence on imported medicines, and on the other to encourage international companies to expand their local presence in manufacturing and/or R&D activities. Countries like China, India, Singapore and Israel have already emerged as leading manufacturers and markets of pharmaceuticals, and in the near future they are likely to become exporters of high added value medicinal products to Europe and the United States. Greater dependence on non-European sources has already raised concerns about the safety and quality of supply in Europe. We must put our manufacturers in a position to compete with these players, without ever abdicating our responsibility for safeguarding health and the quality controls that we have successfully implemented up to now.

The need to ensure high quality standards is particularly felt in the European Union, as low-quality counterfeit medicines can put people's lives and health seriously at risk. The populations of developing countries suffer more severely the absence of proper market surveillance. The European Union and its Member States are actively engaged in multilateral organisations that promote international cooperation; however, on this front as well we would need greater collaboration between Governments, international organisations, pharmaceutical companies and civil society, with the main objective to improve access to quality medicines in developing countries.

1.3.c The European Union's initiatives

Among the major initiatives taken by Europe in this area, we mention the new regulation on clinical trials, the new pharmacovigilance legislation[9], and the revised "Transparency Directive". Specific healthcare funding initiatives are included in the "Health for Growth Pro-

[9] http://www.agenziafarmaco.gov.it/it/glossary/term/1454.

gramme", in the "Horizon 2020" European research programme and in the 2014-2020 structural funds. The next goals identified by the Commission include strengthening cooperation between the EU Member States to leverage economies of scale and pool resources for the systematic implementation and harmonisation of HTA, whose approaches differ widely from State to State and even within individual States (as in Italy).

The threat of deregulation

Implementing and bolstering the European regulatory system and strengthening relations with public authorities of both new and old non-EU competitors will also provide a protection against the constant threats to health from illegal sales networks, counterfeit drugs and active ingredients, bogus cures and speculations on patients' suffering for profit. It is in the loopholes of deregulation, pursued secretly and deviously, that the most insidious dangers lurk.
While the efforts of regulatory agencies should be aimed at simplifying, accelerating and supporting innovation, on the other hand, companies must agree to live in a regulated environment and to recognise this as added value rather than a source of weakness. Pressure to deregulate the system originate from different fronts and often take unexpected courses: sometimes it takes the form of demands from the public opinion, fueled by the emotional wave of hopeless cases (as in the Stamina affair); other times it is conveyed by information that is often superficial and not always ethically correct; or it uses those who should represent the voice and interests of citizens and patients for lobbying or fund raising purposes. All this with the aim of undermining the authority, the credibility and therefore the very existence of the regulatory system.
On the contrary, AIFA – in full agreement with European strategies – believes in few, definite, ineludible rules that are ethical and transparent, in the interest of everyone and firstly of citizens to whom it is responsible for what it does, every day.

2. The challenges of innovation to the regulatory system

Promoting, evaluating and supporting healthcare innovation is a key issue: it is ultimately the condition on which depends access to safer, more effective therapies, and therefore better treatment opportunities and better quality of life for patients. It is a sensitive and complex process that starts with research, development and testing of a treatment in humans; continues with the marketing authorisation of a new molecule and the monitoring of its effects in real-life clinical practice, and feeds back the new information into further research studies. AIFA follows the drug's entire life cycle and, unlike most European and international regulatory agencies, handles both the authorisation and the negotiation phase. In light of this distinctive aspect, the Agency has faced the challenge posed by the introduction of the first next-generation innovative drugs, contributing to the debate and promoting discussion on the definition of innovation, the value that should be assigned to it during negotiations, and how to ensure the future availability of new therapies to all those who need them, without geographical discrimination.

2.7 Access to care, innovation and sustainability. The potential contribution of equivalents and biosimilars

2.7.a The penetration of equivalent medicines

2.7.b Bioequivalence and bioavailability studies

2.7.c Quality, safety and efficacy of equivalent medicines

2.7.d Savings achievable with generics

2.7.e Biosimilars. The new frontier of generics

2.7.f Biosimilars: towards a common European vision

2.7.g The nomenclature of biosimilar medicines

2.1 New scenarios in the authorisation and evaluation of new drugs

2.1.a Peculiarities of the AIFA model

The marketing authorisation for any new drug is issued on the basis of efficacy and safety data: these are provided in clinical study documentation and are usually obtained from controlled clinical trials that have shown efficacy in specific therapeutic indications relative to a comparator product or, where acceptable, to placebo.

In Italy, the approval and marketing authorisation of drugs paid by the National Health Service, and therefore totally free to citizens, is unique in Europe because, unlike the majority of other European countries, it is carried out entirely by AIFA as part of its institutional missions. These include the entire life cycle of the drug, from the different clinical trial phases to approval for reimbursement, from pricing to post-marketing pharmacovigilance, from the definition of prescriptive appropriateness criteria to assessment of the drug's *effectiveness* under real use conditions (the drug's "actual" performance in real-life clinical practice, as opposed to *efficacy*, as demonstrated by clinical trial programmes). All this is achieved through Monitoring Registers and includes traceability, counterfeiting prevention and monitoring, the safeguard of fair access to medicines, monitoring their use and relevant costs, as well as ensuring the achievement of the related financial objectives.

More specifically, within the framework of decisions concerning access to medications, AIFA manages negotiation procedures with the manufacturer for classification in relation to reimbursement by the NHS and pricing, based on the scientific, technical and economic opinion of collegiate bodies that support the Agency, namely the Secretariats (in charge of preliminary investigative activities), the Technical-Scientific Committee (CTS) and the Pricing and Reimbursement Committee (CPR). The opinion expressed by the CTS takes into consideration the comparative assessment of the risk/benefit profile relative to any similar products already available for the same indication, or the possible therapeutic advantage, if the medicinal product proves to be useful for the prevention or treatment of serious diseases or symptoms for which there is no effective therapy.

As for the pricing of reimbursable medicinal products by the NHS, the negotiated procedure between AIFA and the manufacturers is carried out – through the CPR – according to cost-effectiveness, cost per treatment or cost per day criteria, compared with products of equal effectiveness for the same therapeutic indication, assessment of financial impact on the NHS, market share and evaluation of patients eligible for treatment with the new product, price benchmarking and consumption in other European countries. This activity is complemented and supported by survey data on consumption and expenditure provided by the National Observatory on the Use of Medicines (OsMed).

The agreement concluded with the manufacturer, specifying the price and conditions for reimbursement, is then submitted to the Board of Directors for approval and publication in the *Official Journal of the Republic of Italy*.

When a new drug involving a therapeutic advantage is introduced in standard treatments – as a result of a comparative assessment, or in its absence in the case of orphan drugs – a "price premium" can be granted. In most cases, the negotiated products have already obtained registration or marketing authorisation valid throughout the European Union, following assessment by the EMA and a decision by the EC. With the support of specific techniques for the financial assessment of pharmacological treatments (HTA), such as Cost-Effectiveness Analysis (CEA) or Cost-Utility Analysis (CUA), the decision-making process includes the determination of the drug's *cost-effectiveness*, i.e. treatment's value not only from a clinical but also from an economic point of view ("value for money"). This is a more comprehensive process that involves an evaluation of results, expressed in terms of additional health produced, including potential reductions in other healthcare cost items, with a view to optimal allocation of available resources.

This process also identifies and assesses any characteristics of innovation of the product compared to already available treatments. These aspects, which are evaluated during the negotiations, are necessarily accompanied by additional elements inferred from economic impact analyses (*Budget Impact Analysis*) and by non-clinical or economic considerations, such as those pertaining to ethics and equity. The assessment described so far applies to ex-ante evaluations, i.e. the decisions taken at the time of marketing the new drugs. After a few years of use in clinical practice, the clinical and economic assessment of the product can be reviewed ex-post, based on usage and effectiveness data - whether collected through AIFA Monitoring Registers, post-marketing studies or otherwise - and lead to renegotiating the price of the product according to actual use conditions and results obtained.

Last but not least, at the time of negotiating the product's reimbursement and price, following a specific evaluation of uncertainty (defined in terms of safety, effectiveness and economic impact) that can be attributed to the drug being evaluated, AIFA has specific economic risk-sharing tools (Conditional Reimbursement Schemes or Managed Entry Agreements) that allow the NHS to mitigate the effect of this uncertainty through 'pay for performance' mechanisms, or eliminate it altogether through 'payment by results' or 'payment for responders only' schemes.

2.1.b New authorization models

The challenges arising from the new pharmaceutical scenario, particularly the need to support and reward research aimed at innovation and provide timely access to innovative drugs

while ensuring adequate evaluations on the efficacy and safety of these treatments, are making it increasingly convenient to implement new, more flexible approval models already adopted at European level, especially at a time when the procedures are becoming more and more centralised and patient populations increasingly stratified.

For specific cases, a transition is being considered from the traditional approach, which involves extensive trials and marketing authorisation for large groups of patients, to an adaptive approach characterized by the development of innovative clinical trial projects and greater patient involvement in decision making, in order to understand what level of uncertainty they are willing to accept. Promoting early access implies the need, on the one hand, to accept a higher level of uncertainty, and on the other to strengthen cooperation between regulatory agencies, prescribers, patients and payers so as to improve available tools for producing evidence and carrying out more effective real-time monitoring in support of decisions.

The 'adaptive licensing' or 'adaptive pathways' approach, now more accurately known as 'Progressive Patient Access scheme', is a prospective authorisation process that begins with the early authorisation of a medicinal product in a limited population of patients, and continues with a series of iterative phases where evidence is collected and the marketing authorisation is adjusted so as to extend access to the drug to increasingly large patient populations, on the basis of collected usage data and further, broader studies than the initial ones. In a progressive authorisation approach, the economic component of the cost of new drugs must also come into play much sooner, which means starting early on a close dialogue with patients, prescribers, payers and the industry. Right from the start, there should be discussion and integration between the scientific approach, the HTA and the cost-effectiveness assessment, so as to facilitate the transition from adaptive licensing to adaptive reimbursement. Early involvement of industry and the HTA would allow a better positioning of the medicinal product, in the interest not only of patients but also of the system's sustainability. For this to occur, however, all the players involved in the authorisation process should be aware, aligned and in favour of modifying the ethical, regulatory and technological frameworks underpinning such a crucial change in the registration model: from manufacturers to prescribers and global regulatory bodies.

Europe already has a number of regulatory instruments that are well suited to our environment, characterized by significant challenges like drug prices, ageing population and sustainability of healthcare systems. The new framework of the regulatory process is based on four pillars: authorisation in exceptional circumstances, conditioned authorisation, pharmacovigilance legislation, and regulations on clinical trials.

To govern innovation, we need an integrated approach able to leverage scientific evaluations, HTA information and pharmacovigilance data synergistically in a cycle that feeds on itself on an ongoing basis.

The model adopted by AIFA already combines the HTA with the clinical assessment, carrying out risk-benefit and price-benefit assessments in parallel and entirely within the process itself. The information produced in this phase are then validated by the drug's performance in real-world practice through additional evidence collected through monitoring, which is again fed into the assessment process.
AIFA's experience also uses tools like early dialogue with the industry, concerning strictly clinical and regulatory aspects as well as pharmacoeconomic and HTA issues, through preliminary scientific evaluations and mechanisms for conditional reimbursement schemes (Managed Entry Agreements). In this area, AIFA is inclined to adopt the payment-by-results model, i.e. reimbursement of the drug only for patients in whom its effectiveness is produced and proved.
The Monitoring Registers are one of the most effective tools available to regulators; those developed and adopted by AIFA are real dynamic databases that evaluate use of medicinal products in clinical practice.
AIFA's Monitoring Registers currently collect the data of hundreds of thousands of unique treatments at individual patient level, in full respect of privacy. Consulting the Registers allows highly useful information to be generated through real-time access to the database and searches by disease and type of treatment administered, city and even hospital and department, including temporal variations in prescriptions. By the end of 2015, AIFA had put online 125 Registers for 32 Marketing Authorisations (MA) of 107 products with 18 different therapeutic indications (4.1. of the Summary of Product Characteristics, over 650,000 patients under treatment, followed by 24,000 hospital physicians and 1,350 hospital pharmacists registered under the supervision and authorisation of 900 healthcare directors and 48 Regional Authorisers throughout the country. No other public or private healthcare system can rely on a database of this magnitude.

2.1.c Usefulness of early dialogue with companies

In a highly globalised context, the new drug approval process has to take into account a number of challenges: from the definition of increasingly targeted and specific subgroups eligible for treatment to the identification of clear and measurable endpoints. The latter issue is directly related to the harmonisation of clinical trials, not only at European level but also globally, as recently discussed within the framework of the International Coalition of Medicines Regulatory Authorities (ICMRA).
The scientific advice provided in the early stages of a drug's development by the regulatory agency, starting from the design of clinical trials, increases success rates and reduces the

overall time and scope of the objections raised during the evaluation of registration dossiers. It is a key tool to support the development of effective safe, high-quality products, and also protects patients, keeping them from participating in clinical trials that are unlikely to lead to the approval of new medicines.

This is confirmed by an analysis of the results of marketing authorisation applications conducted by EMA. The latest reports showed that in two out of three programmes submitted for scientific advice, the study designs were inadequate to generate data for the assessment of the product's benefits and risks; a study design deemed acceptable by the scientific advisors, or changed to conform to the recommendations contained in the scientific advice, demonstrated higher probabilities of success outcome with success rates of 84% and 86% respectively, compared to 41% of designs that are inadequate or not modified according to the recommendations contained in the SA; compliance with scientific advice on clinical trial design has been associated with a reduction of the main objections raised by the Committee for Human Medicinal Products (CHMP) during assessment of the application and with an assessment process that is 61 days shorter, on average, which means that these drugs can be available to patients sooner.

Some medicines fail to obtain the marketing authorisation because of inadequacies in clinical trial design and inability to demonstrate that the benefits outweigh the risks. According to the EMA, this not only deprives patients of new drugs, but it also means that they can be enrolled in clinical trials not suitable to generate data for regulatory assessment.

The majority of clinical development plans submitted for scientific advice (EMA), before an application for marketing authorisation, have been judged unsuitable for future risk-benefit assessment. The companies that have changed their clinical development plans in accordance with EMA recommendations have had higher probabilities of obtaining a marketing authorisation. The EMA, through the *Scientific Advice Working Party* (SAWP), provides scientific advice to companies during the development of a product to help them plan scientifically valid trials that can generate adequate data for the risk-benefit assessment by the CHMP.

2.2 The "sofosbuvir case"

Sofosbuvir was the first in a long series of next-generation active ingredients with a very high impact on pharmaceutical expenditure to penetrate the domestic and international market, arousing huge expectations in patients for the clinical benefit which promises to be - in some cases at least - no less than the eradication of hepatitis C.

Inevitably, therefore, the "sofosbuvir case" represented for all the parties involved (regulators, patients, physicians, payers, businesses) a crucially important precedent, providing among other things a test bench for public health systems and for national regulatory authorities, and forcefully raising the issue of the appropriate value and price to be assigned to innovation within a global context of sustainable healthcare.

After sofosbuvir obtained the European marketing authorisation in January 2014, the individual Member States started negotiations with the MA holder for decisions concerning price and reimbursability. AIFA was one the first European agencies to reach an agreement with the MA holder (in September 2014), in consultation with the Ministry of Health, to allow patients with HCV progressive access according to clinical urgency criteria.

It is clear that the prospects for the eradication of hepatitis C, in view of the large incidence of the disease in our country, have generated considerable pressure to promote access to new treatments also in the early stages and intermediates of the disease. Such a solution, however, in addition to not being feasible from an economic point of view, is not even supported, as has often been publicly represented by AIFA, by sufficient scientific, regulatory and pharmacoeconomic considerations. In its decisions, AIFA has taken into account the need to consider from the start the entire set of treatments that would soon be available for the same disease, while carefully monitoring the early data from real clinical practice. Between October 2014 and June 2015, AIFA negotiated the other new drugs for hepatitis C that have expanded the range of treatment options, and made them available at the expense of the NHS. In order to support physicians in identifying the most appropriate personalised therapy for each patient, the Agency has also made available and regularly updated an algorithm for the treatment of chronic hepatitis C, developed in collaboration with the Italian Association for the Liver Studies (AISF)[10].

The Ministry of Health has created a special fund for innovative medicines, in addition to the healthcare fund, intended for all therapeutic areas affected by the gradual introduction in the market of increasingly effective innovative drugs. For the 2015-2016 period, a total of 1 billion euros has been allocated, which should enable the Regions to bear the costs of treatment for the more severe cases.

[10] https://www.agenziafarmaco.gov.it/piattaformaAlgoritmi/index.php/771432/lang-it.

AIFA has strenuously defended its negotiation and progressive access strategy and has closely monitored the new treatments, emphasizing the importance of waiting for evidence of the effectiveness of new drugs and of evaluating very carefully their real-life efficacy and safety profile through the data that will emerge from AIFA Monitoring Registers, new studies and pharmacovigilance reports.
The Agency has often publicly clarified the reasons of the choices made and the appropriateness and value of centralised negotiations, and has reiterated the different profiles – scientific, regulatory, ethical and economic – that influence the management of these promising new treatment with a high impact on healthcare costs.

2.2.a From the ethics of profit to the profit of ethics: sofosbuvir as an example of a medicine with an unsustainable cost, a dramatic challenge for health systems and a moral hazard for the industry

July 2014: while in Italy scientific societies and patient organisations wrote to Gilead Sciences S.r.l. (hereinafter Gilead) to ask for broader access to the drug, actions were initiated for the first time in the United States to demand transparency on the determination of the price of *Sovaldi* (the brand name of sofosbuvir) and on possible conflicts of interest of those who defined the treatment guidelines.
After approval of the first of the new drugs for chronic hepatitis C, *Sovaldi*, by the *Food and Drug Administration* (FDA) (December 2013) and, some time later, by the European Medicines Agency (EMA), the leading concern of the States involved in these decisions, and in particular of the regulatory authorities, was to define the prescription and reimbursement that would best ensure timely access to care for those who actually need it and a sustainable cost for the public healthcare budget.
Even before starting the negotiation process with Gilead (the MA holder), AIFA, aware of the importance of this new therapies and of those that would follow in the next few months for the treatment of hepatitis C, adopted a set of special procedures in consultation with the Health Ministry, bringing together the different Committees in a unified session and in dedicated sessions and setting up a permanent discussion table with other institutions, patient organisations, scientific societies and research institutions, with the aim to lay the groundwork for an ambitious pharmaceutical plan for the eradication of hepatitis C in the next few years, starting with *Sovaldi*, but also taking into consideration new drugs under development with the potential to treat hepatitis C patients in a safe and possibly more effective ways, with costs depending largely on the reference price that will be negotiated for sofosbuvir.

The process was suspended until the end of September 2014, as a result of the extension requested by the company, which did not attend the last meeting of AIFA's Pricing and Reimbursement Committee. This decision caused concern among scientific societies and patient organisations, as revealed by a letter sent on 16 June by AIGO, AISF, SIGE, SIMI, SIMIT and EpaC to Gilead Italia, and for information to Minister Lorenzin and to the Director General of AIFA[11].

It is worth recalling that, under an agreement with AIFA, Gilead still supplied the product in Italy on a "free compassionate use" basis, in accordance with Ministerial Decree of 8 May 2003, to thousands of hepatitis C patients in the most urgent cases (i.e. patients with severe relapse of the disease after liver transplant [fibrosing cholestatic hepatitis or chronic hepatitis with METAVIR fibrosis grade>F2] or patients with decompensated cirrhosis who are candidates for liver transplantation [MELD <25]).

Many countries in the world have looked and still look to AIFA with great attention because of our rigorous negotiating approach based on advanced progressive agreement procedures. A recent meeting of all heads of European regulatory agencies has recently confirmed the need for coordination between agencies, aimed at a more effective and consistent negotiation with the manufacturer of the price, which Italy was first to regard as too high.

Not coincidentally, the price of *Sovaldi* raised, great concern in the United States, as mentioned above. Doubts emerged on the criteria used by the company to determine it. A significant initiative was taken by the United States Senate Finance Committee, having jurisdiction on programmes like Medicare and Medicaid, which together provide healthcare to over 100 million Americans and account for nearly 900 billion dollars a year in federal spending.

Committee Chairman Ron Wyden and Committee member Chuck Grassley initiated an investigation and wrote to Gilead Sciences Inc.[12] requesting detailed information on the price of sofosbuvir, which, in the United States and worldwide, has been welcomed as a real breakthrough in the treatment of tens of millions of patients infected with HCV virus. "Given the impact *Sovaldi*'s cost will have on Medicare, Medicaid and other federal spending, we need a better understanding of how your company arrived at the price of this drug" – wrote the two Senators[13].

In order for a marketplace to function properly, it must be competitive, fair and transparent. AIFA understands very well that the value of a medicine never coincides with the cost of its production as such, or simply the value of the milligrams of active ingredient (as has been accurately explained by pharmacoeconomics experts), but it is also important to understand the mechanisms leading to the determination of the final price taking into account, for example, investments in clinical development, trials and reasonable patent protection. However,

[11] http://www.agenziafarmaco.gov.it/sites/default/files/Lett_Congiunta_16Lug2014.pdf.

[12] http://www.finance.senate.gov/imo/media/doc/Wyden-Grassley Document Request to Gilead 7-11-141.pdf.

[13] The recently published results of this ponderous investigation are available at http://www.finance.senate.gov/newsroom/ranking/release/?id=3f693c73-0fc2-4a4c-ba92-562723ba5255.

even taking into account all these considerations, it is unclear how Gilead has determined the price of sofosbuvir, which seems to be much higher than expected even considering the costs of development and production and the very large discounts offered by the company in other countries. All this raises serious doubts as to the effectiveness and rationality with which the issue of the drug's market impact will be addressed from the industrial point of view.

We know that in Egypt, for example, *Sovaldi* has been offered at about 700 euros per 12-week course of treatment, a discount of approximately 98% on the average price requested in Europe. Even taking into account the different GDP and different prevalence of the disease between Italy and Egypt, the price proposed to AIFA by the company would have been twenty to thirty times higher, and therefore financially as well as morally unacceptable. Clearly, manufacturers must have their profit, but at what price?

An efficient pharmaceutical market needs not only innovative medicines but also informed patients and consumers, so as to understand the dynamics of negotiation procedures.

At the opposite extreme, in the United States, the price of *Sovaldi*, was calculated at around 58,000 euros for a standard 12-week treatment, but the FDA documentation shows that costs may be significantly higher for patients requiring longer treatments, as in the case of genotypes 1 and 3. A longer treatment regimen doubles the cost to at least 120,000 euros for *Sovaldi* alone, plus the cost of other drugs used for the combined treatments that are required with this molecule. Moreover, HCV patients with liver cancer may require even longer and more expensive treatments. The large population of patients eligible to be treated with this product and the high cost of each treatment raise serious concerns on the ability of health systems to bear such a burden. According to reliable estimates, in the United States, *Sovaldi* alone could affect Medicare's prescription drug spending by 1.4 billion euros between 2014 and 2015 if 25,000 patients enrolled in pharmaceutical treatment programmes should receive the therapy (10% of hepatitis C patients and about a quarter of diagnosed patients). If 75,000 more entitled patients should receive the medication, the costs of the programme would increase by an additional 5 billion euro. In Italy, the costs would not be much lower, in fact they could be higher.

In light of these data, the two Senators asked the company to produce information and documents[14], including those concerning the merger between Gilead and Pharmasset, the original developer of *Sovaldi*, which Gilead acquired in 2012 for 11.2 billion dollars and which, according to the *Securities and Exchange Commission* (SEC) records, had intended to sell the drug profitably in the United States for $36,000 ($50,000 dollars less then the price at which it is currently sold in the United States). This is why it is difficult understand what led to Gilead's marketing strategies. Additionally, the company's financial statements show that

[14] http://www.sec.gov/Archives/edgar/data/1301081/000119312511331226/d265035dsc14d9.htm.

the Research and Development costs incurred by Pharmasset in 2009, 2010 and 2011 (the period when sofosbuvir was developed) amounted to $176.7 million, of which $62.4 million directly attributed to the development of *Sovaldi*.

Like AIFA, the US Senate Committee is also determined to understand what justifies the difference between the expected and the actual price of the drug and between the price in the United States and that charged or offered in some foreign markets. We would like to be informed in detail of the costs incurred for Research and Development, marketing and advertising (Gilead's advertising and promotional costs have risen from 116.6 million in 2011 to 216.2 million in 2013).

Above all, like the US Senate, AIFA would like to learn about any potential conflicts of interest with the scientific societies who recommended and are recommending the drug. The Oregon Health and Science University has recently reviewed the guidelines for treatment with sofosbuvir submitted jointly by several scientific societies, and concluded that there is a "substantial risk of conflict of interest that influences the recommendations": 18 of the 27 members of the group involved in the development of the guidelines proposed by the American Association for The Study of Liver Diseases[15] (AASLD) and the Infectious Disease Society of America (ISDA) allegedly declared a direct financial relationship with Gilead (which, according to AIFA's conflict of interest rules, is the highest level of conflict) or received institutional funds from the company. Both groups and a third partner, the International Antiviral Society-USA, received funding from Gilead, according to the findings of the US senators.

Therefore, we have all lawfully and publicly asked the company to disclose if and how the commercial success of *Sovaldi*, based on Q1 2014 sales, could influence the prices being negotiated in Europe and worldwide. During nearly all the month of the first year since its global launch, *Sovaldi* recorded sales of approximately 20 million euros per day, or double the expected sales and three times the expected profits. According to financial analysts' projections, Sovaldi would achieve sales of $9 billion by 2017. In March 2014, ISI analyst Mark Schoenebaum revealed that sales of $11 billion would be realised in the first year of launch; this estimate turned out to be fairly accurate, with continuing globally into 2015 thanks to the combination of sofosbuvir and ledipasvir (another Gilead product), which under the brand name *Harvoni* is one of the anti-HCV treatments that do not need interferon and ribavirin. Under these conditions, it is nearly impossible to predict the amount of global revenues during the long years of patent protection of these medicines.

The US senators asked Gilead to disclose the effects on the price of the decision to apply for authorisation to sell single-dose sofosbuvir in combination with other drugs; the estimated cost per patient and per treatment for each FDA-approved regimen based on the different genotypes; what changes are expected over the next 5 years for these regimens; how many

[15] http://www.aasld.org/.

patients have been included so far by Gilead in its care programme, which provides discounts to reduce co-payment costs (according to the company's estimates, 30,000 patients would be treated in the first quarter); what are the specific eligibility criteria; what is the list of countries where sofosbuvir will be sold and the price planned for each. The US Senate gave Gilead 60 days time (until 11 September 2014) to answer all the questions. Patients do not have the luxury to wait that long: AIFA would have wanted to have them right away, so that such a large and unexpected profit could be returned to the community immediately, in the name of a true, superior sense of social responsibility.

As mentioned above, innovative hepatitis C treatments are being introduced on the market, one after the other, as was expected. Sofosbuvir was only the first one in chronological order, but other molecules and drug combinations have already been approved in Europe (and in the United States) or have received a positive opinion from the EMA's CHPM. We are talking about products that have significant therapeutic potential, high costs, and are all covered by patents with terms of more than ten years.

From January 2014 (when sofosbuvir was authorised for marketing in the European Union) to the present, the market for hepatitis C treatments has ceased to be monopolistic. Research and clinical studies in this area (and soon also in other areas, primarily new CNS drugs and anticancer and antidiabetic agents) are finally providing patients with increasingly effective, easier to administer and potentially safer treatments which, in some cases (including hepatitis C), promise to eradicate the disease.

As remarked above, for public healthcare systems, whose solidity is likely to be sorely tested by the wave of new medicines, the commitment to ensure full coverage of patients who need this type of therapies requires shared but rigorous choices in assessing innovation and added therapeutic benefit, determining prices, identifying criteria for progressive access to drugs, and conducting post-marketing monitoring of efficacy and safety profiles in real-life clinical practice.

AIFA, in consultation with the Ministry of Health, has chosen to privilege public debate involving patients, physicians, scientific societies and manufacturers; has engaged in dialogue with other national agencies to identify shared strategies. It has asked all stakeholders to consider the "sofobuvir case" described above not as an isolated event that elicits hasty responses influenced by emotion, but rather as an opportunity to experiment with new models able to address the changing global context of pharmaceuticals according to a scientific, regulatory and economic approach but also taking into account ethical and social considerations.

AIFA was the first European agency to address with great determination the issue of the price of *Sovaldi* (but the same also happened in the United States)[16] and to consider the manufac-

[16] http://www.agenziafarmaco.gov.it/it/content/dall%E2%80%99etica-del-profitto-al-profitto-delletica-sofosbuvir-come-esempio-di-farmaci-dal-costo-i.

turer's initial request excessive and unacceptable from an ethical as well as financial point of view, publicly inviting Gilead to reconsider the proposal, also in light of the unexpected profits that promised to flow in from sales of the medication. Profits that are actually being realised. According to the company's report[17] on financial results for the third quarter of 2014, to date approximately 117,000 patients have been treated with *Sovaldi*, and the product's launch in December 2013 increased by more than $3 billion the company's sales of antiviral product compared to the same period in 2013. Specifically, sales of *Sovaldi* in the third quarter ($2.8 billion, of which 2.2 billion in the United States, 523.5 million in Europe and 73 million in other countries) – increased to $8.5 billion the sales revenues achieved by the company thanks to this product in the first nine months of 2014 (7.3 billion in the United States, 1.1 billion in Europe and 134.5 million in other countries). According to some financial analysts, the projected revenues from sofosbuvir in the first year of launch amounted to $11.3 billion, i.e. over 10 times the results that their best molecules have achieved so far in their first year of marketing. This is equal to $944 million per month, almost $31 million per day, or approximately $1,300,000 per hour. Figures that make one think. Or at least, that make *us* think.

In conducting the negotiation with the company, AIFA has never focused solely on sofosbuvir, which at the time of starting negotiations was, as mentioned, the only product on the market, but took into account new drugs in the process of being registered, which would provide valid therapeutic alternatives and whose costs would largely depend on the reference price negotiated for sofosbuvir. AIFA's strategy – which other countries observe with careful attention – has been aimed from the very beginning at laying the groundwork for an ambitious pharmaceutical plan to eradicate hepatitis C over the next few years. This allowed the Agency to close the deal for the reimbursement of *Sovaldi* within the time frame requested by the Ministry of Health, so as to allow the treatment of largest possible number of patients at a lower average piece than in the rest of Europe, given the higher prevalence of the disease in Italy and the close correlation between the two parameters (price and volumes). Progressive appropriateness criteria have been specified by the Technical-Scientific Committee, after listening to the voice of patients and to the opinion of specialists.

As mentioned previously, the enormous burden of hepatitis C drugs for public healthcare budgets is closely related to the prevalence of the disease among the population. Clearly, the arrival of other anti-infective agents, medications for Alzheimer's, pre-Alzheimer's and dementia in general, new anticancer, antidepressant and antidiabetic drugs (just to name a few), also intended to be administered to hundreds of thousands of patients, the public system as a whole risks structural impacts that could potentially cause its collapse. Yet, preventing patients from accessing real innovation or precluding their hopes of a cure is unthinkable.

[17] http://www.gilead.com/news/press-releases/2014/10/gilead-sciences-announces-third-quarter-2014-financial-results.

Reconciling the promotion of research and competitiveness and support to innovation with access to new drugs and system sustainability is a daunting task, especially in a situation like that of Italy in which the State bears the burden of over 70% of drug spending and aspires to continue to provide healthcare based on principles of universality and solidarity. Maintaining this balance requires an ethical reflection on the system of values of society in general. Decision makers are responsible for determining how much we are willing to pay for what; manufacturers for setting the level of profit, which is unavoidable for truly innovative products intended for large populations; prescribers and patients are responsible for finding an equitable compromise between everyone's right to treatment, taking into consideration the ethical and social relevance of the "products" in question and the actual possibility of their being absorbed by the market and reimbursed by public systems.

2.2.b AIFA: for hepatitis C the goal is disease eradication with a long-term national plan

The eradication of hepatitis C using innovative drugs already on the market and others that will become available in the next few years, is a priority objective of the organisations in charge of protecting the health of all Italian citizens, primarily the Ministry of Health and the AIFA. The process that AIFA and the Ministry have pursued for several months now is based on meticulous planning, in scientific as well as financial sustainability terms, aimed at eradicating the disease at national level and establishing of a Government-sponsored fund to ensure innovative treatments to the more seriously affected patients.
As has been recalled on several occasions, resources have been identified to treat about 50,000 patients in life-threatening conditions due to disease progression; to bear the expense, 1 billion euros has been allocated in the first two years by multiplying by ten the amount of the innovative medicines fund existing so far.
However, the overall plan for the eradication of hepatitis C will have a duration of at least 6-8 years, during which time it is hoped that a better definition of the eligible patient population will be possible through the adoption of screening tools that will highlight the presence of the virus before the disease develops.
The effectiveness of the approach chosen by the central institutions was further confirmed in a study by the University of Tor Vergata, which showed how the eradication of HCV is a goal that can only be achieved in the long term, certainly not in a few months and not without accurate analyses and planning, and a nationwide coordinated effort that responsibly identifies the financial resources and overall sustainability of the NHS with a degree of certainty. It is therefore inconceivable to think that the goal of hepatitis C eradication can be achieved through actions conducted at the local level: this has been confirmed by our Tor Vergata col-

leagues, who have stressed the importance of mass screening to be performed countrywide in order to determine the actual size of the infected population.

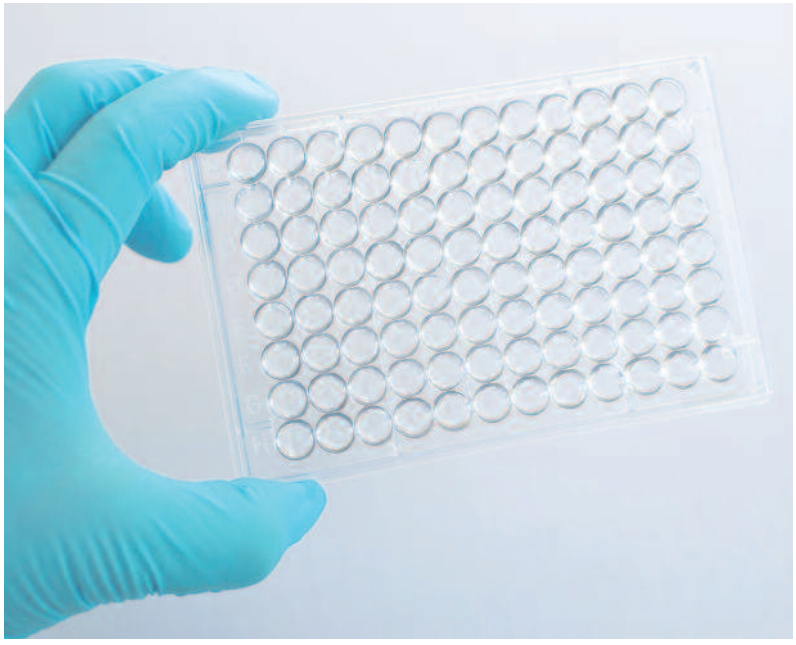
2.2.c Hepatitis C: toward a clinically appropriate and financially sustainable therapeutic approach

In order to contribute to the ongoing and sometimes heated debate on therapies against hepatitis C virus (HCV), we should first provide an objective representation of context data. The first one of these is that chronic hepatitis C has a low mortality rate, and therefore the notion of miracle life-saving drugs is only true for a small though very important proportion of patients. Relatively low mortality is a fortunate circumstance for Italy, which – unlike the rest of Europe – still has areas of high prevalence as a result of the spread of the infection mainly in the 1950s and 1960s. This data is certain: if it were not so, in Italy HCV would have produced countless numbers of victims.
Still, the total number of patients infected with HCV (not entirely known: this data is uncertain) is a significant health issue in all Regions, with differences in the percentage distribution of a disease estimated to be responsible for about 8-10 thousand deaths per year. Another not entirely certain data concerns the temporal distribution of the infection: a large number of patients have lived with it for decades (often without knowing it) and is now in the advanced stages of the disease, i.e. advanced fibrosis or cirrhosis. Experts estimate that approximately 40-50% of HCV-infected patients treated by the National Health Service are in a state of advanced disease (this data is reasonably certain). Based on these few premises, the therapeutic approach, from a relatively uncertain but still scientifically solid and economically sustainable perspective aimed at reimbursing hepatitis C treatments, should be centered on the disease rather than the viral infection. The theory according to which achieving Sustained Virologic Response (SVR) or eradicating the HCV virus is the equivalent of treating all patients is incorrect as well as pharmacologically and clinically inappropriate (in addition to causing a financial loss to the NHS). This is due to the fact that health needs differ greatly between patients with mild or moderate hepatic impairment and patients with advanced liver damage or cirrhosis. While liver function remains intact in patients with mild/moderate hepatitis, the highest risks in terms of development of complications, liver cancer and mortality occur in people with cirrhosis of the liver. It is well established, from a clinical and scientific point of view, that 70% of cirrhotic patients' mortality at 5 years is due to liver disease and that the onset of a complication reduces by 50% the probability of survival at 5 years (certain data). Given these facts, the introduction of new treatments for hepatitis C virus provides a historical opportunity to change the immediate fate of some patients. Some, but not all and not all at

the same time, as this would be a clinical as well as a financial mistake. Two main considerations should be made in order to understand the significance of these therapies:

1. Progressive introduction of several therapeutic agents;
2. Knowledge of liver disease and how it is affected by the eradication of the infection.

Today, referring to sofosbuvir as "the cure" for hepatitis C is already obsolete. Therapeutic combinations that do or do not include its use are by far more effective (in genotypes 1, 3 and 4) than sofosbuvir alone with ribavirin. Although direct comparison studies are not yet available, these evaluations are supported by the fact that real-life study data (TARGET, Hepater Cohort) show that the rates of sustained virological response at 12 weeks after completion of treatment (SVR-12) do not differ significantly from the data of registration trials. As reported by recent technical commentaries (GIMBE, AISF etc.) and in view of the considerations above, any surrogate endpoint, in this case SVR, should therefore be interpreted with caution and attention. For example, it is known that the achievement of this outcome is associated with a significant difference in 10-year survival of cirrhotic patients, which is 30% lower in patients who have not eradicated the infection (one thing that should be mentioned is that it cannot always be eradicated, and not in all patients). A similar correlation is observed for the probability of developing complications.
Even wanting to address the issue from a *Health Technology Assessment* perspective, the analysis should start from the principle of the benefit of the treatment, whose value to the patient (and incidentally to the NHS) is related to the probability of reducing the extent of liver injury and not to the infection itself.
Infection eradication produces its maximum benefit in cirrhotic patients, as it minimizes (but it does not eliminate) complication and mortality risks. Treatment is also significantly beneficial in non-cirrhotic patients with advanced fibrosis, for whom the likelihood of progression to cirrhosis is mainly the result of the persistence of viral infection. The benefits of treatment are very different for patients with mild disease, because in this case it is a function of the probability of progression in the long term, rather than of liver damage in itself or of SVR-12 as such. This is why, in this scenario and given the still rapidly evolving pharmacological and therefore therapeutic situation, the elements of uncertainty and individual variations, the most sustainable strategy from a clinical as well as financial standpoint, is the one indicated by the AIFA Committees, which is now being imitated by other European countries. Clinical, not political considerations dictate evaluating the disease, its characteristics and stage of progression, rather than focusing on the infection. In other words, from a clinical point of view



the value of treatment varies according to the risk incurred by patients: this was the principle underpinning the choice to support higher, but not extravagant costs, to allow fast access to patients at higher risk. This process undertaken by AIFA also has a strong ethical connotation, because it significantly reduces the risk of complications and death.

Indiscriminate massive eradication has no scientific meaning and is unnecessarily expensive, at a time when new treatments are already entering into competition with one another with presumably lower costs. It is certainly desirable to prepare plans for the eradication of HCV, but in order to develop them we would need a large amount of not yet available information on new products. The new AIFA Registers allow us to track the (presumably high) effectiveness of the new anti-HCV agents, in real time and at the level of individual patients. For the time being, however, we cannot say with any certainty which of the regimens is better than the other, in the absence of comparative studies. Another significant element is the unavailability of data on what happens to non-respondent patients, both in terms of liver disease progression and, more importantly, of virus sensitivity to subsequent treatments, because resistance profiles are still essentially unknown.

Even if we assume realistically that the proportion of non-responders is only 5-7% of cases, this percentage is small compared to the cohort of patients with advanced disease, at high risk unless they receive treatment. On the other hand, this percentage is significant if it refers to a very large number of people, including subjects whose disease may never progress or may progress so slowly that it does not give rise to more serious problems. The same type of analysis should be carried out for side effects, which are probably few but, once again, their seriousness varies depending on the severity and stage of progression of the disease.

In view of all these considerations, even assuming that in some cases it may be legitimate to call a tender at local level, from a clinical point of view it would be a dangerous leap in the dark,for which someone would have to take all responsibility. Additionally, from an economic point of view it would be far more advantageous to carry out such a procedure at national or better at European level, as argued by Minister Lorenzin in her closing speech at the end of

the Italian Presidency period. To say that all this, while desirable, would involve a laborious and time consuming process is part of a mindset that no longer belongs to a modern, international regulatory agency, open to discussion on major issues related to the ethical responsibility[18] and regulatory innovation[19] of the pharmaceutical industry.

It is therefore paradoxical that some are trying hard to find treatments that will "cure all" hepatitis patients, while others "forget" to treat those who are eligible according to the criteria established for all Italian citizens.

[18] http://www.agenziafarmaco.gov.it/it/content/il-sofosbuvir-come-%E2%80%9Ccaso%E2%80%9D-dei-nuovi-farmaci-equilibrio-tra-etica-economia-e-profitto.

[19] http://www.agenziafarmaco.gov.it/sites/default/files/rassegna/05-11-2015 - Domenica - Il Sole 24 Ore - Int. Pani - Comitati etici. Uno ma buono.pdf.

2.3 The "*Avastin-Lucentis* case": does the price of a medicine reflect the milligrams of active substance or the value of the clinical outcome?

A. Messori e M. De Rosa, 13 March 2014

2.3.a Pricing mechanisms

Drug pricing mechanisms follow two main philosophies/criteria: on the one hand, the historically obsolete principle according to which the expense for a medication represents the purchase of the raw material that constitutes it (raw material criterion): according to this philosophy, the price of the medicine "pays" for the milligrams of active ingredient needed for treatment, so that the price increases in direct proportion to the amount of active ingredient (and vice versa). According to the other criterion, the price is determined on the basis of the extent/size/importance of the clinical benefit generated by the treatment (benefit criterion). In English-speaking countries this is known as value-based pricing, and the terms benefit, clinical outcome, clinical value, therapeutic value, and so on are used more or less interchangeably to indicate the main parameter used to calculate the price. This philosophy recognises that the driver of economic profit is the extent of the clinical benefit: therefore, the greater the benefit the higher the price.

Known issues in determining value-based prices

The major flaw of the benefit criterion is that, in some situations, the decision maker experiences understandable reluctance if the drug proves to have outstanding clinical efficacy, but is manufactured from a chemically very simple and cheap substance (for example, an inorganic active ingredient already available at low cost in the chemical product market). A known case is that of arsenic trioxide (Trisenox 10 mg ampoules), effective in prolonging the survival of patients with acute promyelocytic leukemia, while consisting of a chemically very simple compound, widely available at a low price. At the time, Trisenox posed a difficult choice for the Agency, because of the enormous difference between the price estimated according to the cost of the raw material (less than 10 euros per ampoule) and the price charged by the manufacturer on the basis of benefit (895 euros per ampoule). It was not possible to reach an agreement between these two extreme values, and the product was therefore placed in category C. Similar cases are very common, particularly in the area of orphan treatments (antibiotics for cystic fibrosis, injectable NSAIDs for ductus arteriosus closure, treatments for Lambert-Eaton myasthenic syndrome, caffeine in ampoules in premature infants, etc.).

Excessive disparity

A short note published on March 11, 2014 on bmj.com[20] analyses the "Avastin-Lucentis case" (and the related dispute over prices). In particular, the note discusses the disparity that exists for these treatments between the price determined according to the raw material criterion and that based on the benefit criterion.

In the clinical practice of the last few years, the prices of these two intravitreal treatments have been approximately 700 euros per injection for *Lucentis*, versus about 70 euros per injection for off-label bevacizumab. As is known, the issue is further complicated by the number of alternatives available in the class of anti-VEGF drugs (bevacizumab, aflibercept, ranibizumab) and that these products are approved both for oncological indications (e.g. colorectal cancer) and ophthalmologic indications (e.g. Age-Related Macular Degeneration, AMD). Out of all anti-VEGF drugs, only aflibercept (trade names: *Zaltrap* and *Eylea*) has the credentials, from a regulatory point of view, for both indications. The oncological version of aflibercept (*Zaltrap*) has a cost per mg of 9.45 euro, while the ophthalmological product (*Eylea*) costs more than 300 euros per mg. Therefore, the cost per mg of aflibercept differs about 30 times between one indication and the other. The systemic treatment of a cancer patient obviously requires a much higher dose than is necessary for an ophthalmological patient (treated topically with a very small amount of active ingredient). So in terms of costs, a cancer patient treated with *Zaltrap* costs a total of approximately 23,000 euros (assuming a "typical" number of treatment cycles), while a patient with AMD, if treated with 10 doses of Eylea, which costs around 7,000 euros. The other anti-VEGF agent with and oncological indication (bevacizumab-*Avastin*) costs no less than 23,000 euros per patient; in turn, the other anti-VEGF with an ophthalmic indication (ranibizumab-*Lucentis*) also costs about 7,000 euros per patient.

Within this reference framework, therefore, the spending levels stand at not less than 20,000 euros per patient for cancer treatment and around 7,000 euros per patient for ophthalmic treatment. Among other things, the question arises whether the proportion between these two benefits is acceptable, since two months of survival with colorectal cancer are worth 20,000 euros while improved vision in over 30% of patients is worth 7,000 euro. The question arises because, on the one hand, remuneration for the oncology indication may seem excessive, while 7,000 euros appears to be underestimated for the ophthalmic benefit. On the other hand, the raw material criterion completely overturns all reasoning of this kind, as preserving vision ends up being worth a few euro, certainly not 7,000 euros per patient.

[20] Messori A., De Rosa M. "Imagining the cost per injection of on-label bevacizumab given for age-related macular degeneration (Rapid Response)", bmj.com, 11 marzo 2014.

The conflict between criteria

This being the situation, how can we determine the price of bevacizumab when administered off-label as a treatment for AMD? The clinical criterion places the cost of intravitreal bevacizumab at the level of both competitors, ranibizumab and aflibercept (about 700 euros per injection, i.e. 7,000 per patient). Instead, according to the cost per mg criterion bevacizumab would be priced at 70 euros per injection (i.e. 700 euros per patient). As in the case of arsenic trioxide and other orphan treatments mentioned above, it is evident that in the bevacizumab vs ranibizumab matter the two criteria – raw material and clinical benefit – appear to be in strong conflict with each other.

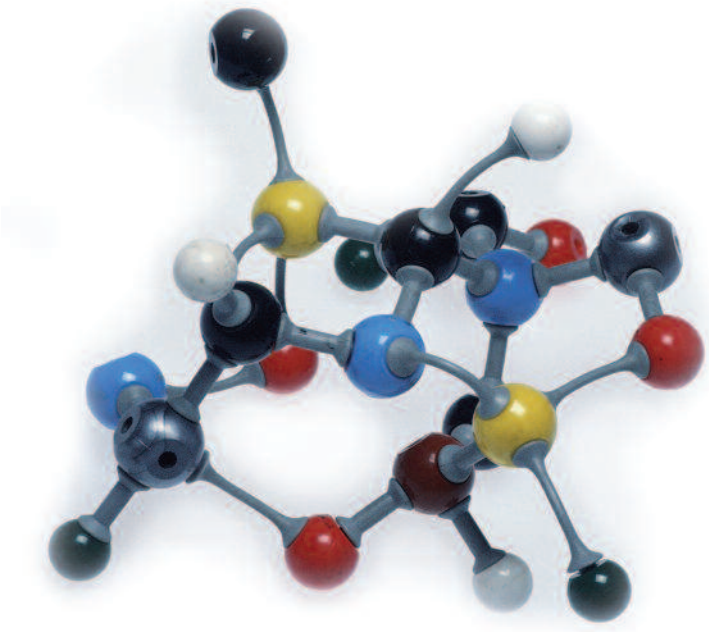
Value-based pricing is the solution

So, which of the two criteria should be given priority? Should a compromise be found? The issue remains a thorny one. As we have seen, an answer - albeit too oriented towards a search for what is theoretically "right" - may come from the analysis of the following hypothetical scenario. Let us imagine that the manufacturer of *Avastin* decides to apply for the intravitreal indication and attends a CPR meeting to negotiate an alleged new product for intravitreal administration. In such a negotiation, 700 euros per injection would be too much (since research on intravitreal bevacizumab was independent), but on the other hand, 70 euros per dose would be too little, as such a low price level would discourage any further research into this disease. In conclusion, this affair emphasises the need to align Italy with the debate current underway in Europe about value-based pricing. In particular, we will need to develop a set of comprehensive rules, and this seems to have priority over one-off, fragmentary decisions proposed as exceptions to be applied to individual cases.

2.4 Oncology medications: making room for high-value innovation

G. Fasola, President of CIPOMO, Director of Udine University Hospital's Department of Oncology, 24 April 2015

Making predictions is often difficult, but available indicators suggest that the discipline of oncology is about to undergo substantial changes. We are probably on the verge of a new phase of the era that started fifteen years ago: immunomodulatory therapies and second-generation molecular targeted agents offer something more than a promise.



Rumours anticipating ASCO's next International Conference in Chicago and already published data encourage new hope for patients. Longer progression-free survival in metastatic lung cancers or potential "recoveries" in advanced melanoma would have appeared unrealistic ten years ago: today they are topics for discussion.

Medical science has advanced, at a more or less fast pace, in all disciplines, and improved expectations for cancer patients reflect advances in diagnostics, surgery and supportive care. However, it cannot be denied that the growth in molecular biology knowledge and massive investments in pharmacological cancer research are outliers. In 2015, oncologists often feel worn out: increasing prevalence, changes in social and cultural context, and the country's economic difficulties have defeated the resilience of many. At the same time, however, new hope is linked to more effective, less toxic drugs open up every day.

Faced with these new possibilities, we would never have imagined we would have to ask ourselves whether the universal health service known so far could afford the cost of treatments. Although it was later put into perspective, the story of sofosbuvir for hepatitis C acted as a detonator; what is about to happen in oncology is likely to be even more disruptive: we cannot resort to a special law for each new drug. Therefore, we need to be methodical in making room for value innovation. Three changes in approach might help:

1. Determine, with as close approximation as possible, the innovation sustainability level that the country can accommodate: this is the responsibility of public institutions, not of health professionals;
2. Make the assessment of the incremental cost-effectiveness ratio binding for new registrations, and review old registrations in light of new knowledge;
3. Discuss more openly with our patients in an advanced stage, the alternatives to an additional line of treatment. Reliable studies confirm that more realistic information helps to choose with greater awareness the best supportive treatment, reducing a pointless use of resources (still quite common) that often fails to prolong survival and worsens the quality of life.

The problem is complex, but many experts agree on these three points: perhaps it would be worthwhile to test them before surrendering to the more or less explicit rationing that in part we are already seeing.

2.5 The five-billion-dollar protein and the future of drug development

Let us imagine the amount of work that precedes the launch of an automobile, from developing the best aerodynamic solutions to building a new, efficient engine, discovering new materials, and defining the various engine sizes and sales prices. Let us now assume a new set of variables. The average time to bring the new car model from the designer's desk to the dealer's floor ranges from 12 to 13 years; only 1 or 2 prototypes out of 10,000 successfully pass the necessary tests; investments that are needed to ensure that research turns into a physical vehicle amount to nearly five billion dollars (for an individual model). Based on these elements, what value would you give a car built in this way? Actually, these figures do not refer to the automotive but to the pharmaceutical industry, the discovery of new molecules[21] and the complex process through which safe and effective medicines are brought to patients. In a series of articles published in Scientific American[22], Ashutosh Jogalekar describes the long and arduous journey from the discovery of an active molecule to the marketing of a product. Drugs are expensive, according to Jogalekar, because the discovery of a new agent is an enormously challenging scientific achievement and requires many years of application.

It is an activity with an extremely high coefficient of difficulty, in which the failure rate is around 95%, all due to the difficulty of finding and influencing, for example, the behaviour of the "right" protein.

Many diseases are caused by abnormal production of proteins involved in different cellular functions, and medicines act, inter alia, by binding to proteins to change their function, but it is difficult to determine exactly which proteins are directly involved in a particular disorder. It takes a number of investigations and experiments to establish whether a protein is among the leading causes of a disease. If one of them is detected, it may not actually bind to a small molecule of synthetic or biotechnological origin so as to be modulated and controlled by the medication. It is challenging to identify a protein even after examining millions of natural and artificial molecules. Once they are past this stage, scientists have to proceed by trial and error in order to transform it into an effective product: a product with the right balance of hydrophobic and hydrophilic characteristics that will allow it to enter cells, and able to counter the activities of protein systems active in the cell wall specifically to keep out foreign compounds.

In short, we could say that the main obstacle to pharmaceutical research is the complexity of human biology, the result of millions of years of evolution. Even though over the past century we have seen great advances in the field of biology, chemistry and medicine, we still

[21] http://www.efpia.eu/uploads/Figures_Key_Data_2013.pdf.

[22] http://blogs.scientificamerican.com/the-curious-wavefunction/why-drugs-are-expensive-ite28099s-the-science-stupid/.

have a long way to go to provide patients with medicines that are always effective and have few side effects.

It should be clarified, however, that the pharmaceutical industry's investments in R&D are not the only factor that determines the final price: many others contribute to its formation, including the frequently mentioned promotional and marketing activities. It is important to recall that unknown quantum of industrial risk that is too often forgotten when discussing Research and Development of medicines and their economic impact, still too closely linked to old business models. In all likelihood, the independent scientific community itself will find answers to the dilemma of the staggering costs associated with drug development.

A very clear example of this is James Bradner, an oncologist at the Dana-Farber Cancer Institute who in 2010 decided to test an absolutely innovative way to accelerate the discovery of new cancer treatments. In 2010, Bradner and his team identified a molecule, JQ1, with the potential to treat a rare form of cancer. The main characteristic of this molecule, a bromodomain inhibitor, is the ability to turn off the growth genes of cancer cells: this makes them "forget" they are cancer cells and start again acting like normal cells.

Instead of patenting the discovery and keeping the details secret until commercial development, Bradner's team[23] opted for crowd-sourcing: they sent samples of the compound to interested laboratories worldwide and made the formula available, after publishing their initial findings in *Nature*. JQ1 was sent[24] to some 300 laboratories, 6 competing pharmaceutical companies and 4 governments, with an average of 2-3 requests per day. The potential of free cooperation between scientists remains to be demonstrated, but it is a stimulating and potentially revolutionary approach.

In a research project jointly conducted by teams from the United States and the United Kingdom, researchers led by Prof. Peter Coveney demonstrated[25] that it is possible to scan a patient's genome sequence, use it to build the three-dimensional structure of one of his proteins, and "match" it with the most effective medicine among those available for a specific disease. In other words, a few hours of calculations performed by "super computers" could replace years of laboratory experiments, enabling us, in the not too distant future, to produce more effective and less expensive drugs.

[23] https://www.youtube.com/watch?feature=player_embedded&v=70ua-1e9YN0.

[24] http://www.cleveland.com/healthfit/index.ssf/2013/08/heart_failure_breakthrough_may.html.

[25] http://www.bbc.com/news/science-environment-26213522.

2.6 Innovative medicines. The future of sustainability is in price negotiation at European level

The national pharmaceutical spending, controlled with difficulty by limits that have probably become inadequate and a dichotomy between hospitals and the territory that needs reconsidering, can no longer guarantee accounting balance and stability. This means that overall strategies are necessary to overcome the current limitations of federalism in healthcare and reach beyond national borders.

In the face of the momentous transformation that is revolutionizing the world of pharmaceuticals, public health systems should be reconsidered as a whole, from an increasingly integrated and less local perspective. We need to take into account the values and economies that, in a globalized world, originate from networking, information sharing, experiences and development and sustainability policies.

Within this framework, different interests converge into a single goal from which all stakeholders (patients, businesses, researchers, and the public system) can benefit: the availability of more effective treatments and a model that will guarantee access and bear the costs. AIFA, as agency involved in both the drug approval and the negotiation process, is applying a set of advanced tools for pharmacoeconomic assessment of pharmacological treatments (HTA), risk sharing with pharmaceutical companies (MEA), and constant monitoring and reassessment of the risk-benefit and benefit-price profiles of medicinal products (Monitoring Registers). However, as pointed out by Health Minister Beatrice Lorenzin, additional information is required. For example, updating the National Formulary as part of the new "Covenant for Health" is an important milestone for the governance of pharmaceutical expenditure. The guidelines contained in the Covenant include the possibility for AIFA to adopt reference prices for products that have the same therapeutic potency, whether their patent is expired or is still in force; a revision of the national regulation so that reimbursement is defined simultaneously with the issue of the marketing authorisation, periodic review of negotiating agreements (the authority to renegotiate with pharmaceutical companies a lower price for a biotechnological product the day after its patent or complementary protection certificate, in the absence of a concomitant price negotiation for a biosimilar or therapeutically comparable product, and the price of a medicinal product subject to conditional reimbursement after at least two years of marketing when the benefits evidenced by AIFA Monitoring Registers are lower than those expected and certified); the definition of a process to ensure support solely to real therapeutic innovation; simultaneous applicability of AIFA's decisions throughout the national territory.

In Italy, we still have 21 regional health services, with a fragmentation which makes it difficult to ensure equitable of access to healthcare for all citizens. Such a system can be improved

through simplification and efficiency, starting from clinical studies: streamlining the procedures, rationalising Ethics Committees and investing in specific professional profiles could be the steps leading to a new era of research in Italy. A similar approach should be adopted when negotiating prices and managing purchases: a National Pharmaceutical Fund, separate from the National Health Fund, would help centralise negotiations and create single purchasing centres at the national, or better at the European level. These solutions could bring significant savings of resources and a more equitable access to treatments.

Italy was one the first European countries to address the wave of high-cost, innovative drugs. Sofosbuvir opened the way for other next-generation medications for hepatitis C. New molecules for the treatment of certain forms of cancer and Alzheimer's disease will follow.

In recent months the Agency, through cooperation with manufacturers, has been able to provide patients with some of these new products on a compassionate use basis, even before settling the matter of prices and reimbursement. Afterward, it negotiated competitive prices with the MA holders leveraging, in the case of drugs for hepatitis C, the high prevalence of the disease in our country compared with the rest of Europe. Nevertheless, it was necessary to enforce an extraordinary ad hoc instrument for these products to be purchased by public healthcare facilities and given to patients in serious conditions. As mentioned above, Minister Lorenzin has made commitments for the establishment of a specific fund for innovative drugs totalling 1 billion for the 2015-2016 period, which will allow us to treat the more severe emergencies.

However, a broader reflection will need to be initiated on the basis of discussion and cooperation at Community level. This need had already emerged, prompted by inputs from Italy during the country's term of EU Presidency. During that period and on subsequent occasions, discussions were carried out on the advisability of negotiations at European level that can use the advantage of large numbers, while respecting the different approach of each individual State. Such an ambitious project requires sharing data and experiences and a willingness to converge on common solutions, overcoming the resistances shown so far by some European countries.

The nature of healthcare systems in Europe is highly diverse; in this context, Italy is committed to maintaining the peculiarity of its healthcare service, which stands out for its being based on principles of solidarity and universality. However, the Italian experience can suggest case studies and good practices that can be implemented at European level as well.

2.7 Access to care, innovation and sustainability. The potential contribution of equivalents and biosimilars

2.7.a The penetration of equivalent medicines

In a context of rationalisation and optimisation of healthcare resources, promotion of pharmaceutical innovation and extended access to care, a key role is played by medications that have no patent coverage or whose patent is expired. By 2017, the last major generics of chemical synthesis drugs will come to an end; therefore, in the coming years the savings that can be obtained from loss of patent coverage will derive mainly from biologics[26].

However, it will be crucial to continue promoting the knowledge and dissemination of equivalent medicines, whose regulatory evolution and cultural acquisition have been slower in Italy compared to other parts of Europe.

It should be kept in mind that in Italy a large portion of the active substances available on the market (approximately 80%) have benefited from considerably longer patent coverage than in other European countries[27].

Consequently, the possible savings for the NHS resulting from the loss of patent coverage, have also been delayed over time, precisely because of the inability to market generic medicines have long been available in the rest of Europe.

In Italy, the body of regulations governing medicinal products not covered by patent rights has grown significantly since 2000. The *transparency lists*, i.e. lists of products whose patents have expired and the corresponding reimbursement prices, were first published in 2001, and are currently updated by AIFA and made available on the Agency's website.

Over the years, several aspects relating to the regulation of these drugs have been strengthened and further clarified with interventions aimed at reducing prices and achieving faster access to the market. Recently, the entry into force of the Balduzzi Decree and the Ministry of Health's implementation decree of 4 April 2013 led to an acceleration of the procedure for the approval of generics and biosimilars. If a pharmaceutical company offers, for an equivalent based on an active ingredient that has never been negotiated, a price that is clearly advantageous to the NHS, AIFA forwards the relevant documentation directly to the Board of Directors, and the Agency's Pricing and Reimbursement Committee subsequently

[26] A recent study estimated at about €1.10 billion the maximum total savings that can be generated by the introduction of generics from now to 2020, assuming that prices will evolve in the same way as has been seen so far following the introduction of generics. The recent GFK Report has estimated a reduction in expenditure of 25% thanks to savings from the introduction of the biosimilars of three biologic agents (adalimumab, bevacizumab and etanercept).

[27] Complementary Protection Certificates (CPCs), established in 1991, allowed the extension of patent coverage of medicinal products, initially determined to be 20 years, for a maximum of 18 additional years after the natural expiry of the patent, thus making it possible to exploit the molecule exclusively for up to 38 years. Subsequently, in order to mitigate the negative effects mentioned above, a measure was introduced for the progressive adjustment of the CPC duration to that of other European countries.

acknowledges the decision. Submission to the Technical-Scientific Committee is only required if the generic manufacturer applies for reimbursement not only for packages identical to those of the originator, but also for packages with a different number of doses and/or different quantities of the already negotiated active ingredient.
Streamlining administrative procedures is an important aspect, but not the only one. As mentioned earlier, cultural resistances - in part still in place - have slowed down the penetration of drugs to with expired patents. The term "generic", which refers to drugs that are copies of brand-name products no longer protected by patents, has probably helped to generate in the public a sort of mistrust towards these medicines, which should be more accurately described as "equivalent", in reference to the requirement of bioequivalence, essential for marketing authorisation. Aware that scientific knowledge plays a crucial role in support of physicians' prescription decisions and patients' treatment compliance, AIFA has been committed for years to promoting and conducting a series of initiatives to inform and raise awareness among the public and healthcare providers on expired patent drugs. One of these is the recent publication of the in-depth document "Equivalent Medicines. Quality, safety and efficacy"[28].

2.7.b Bioequivalence and bioavailability studies

The definition of equivalent is contained in Directive 2001/83/EC of the European Parliament and of the Council, also known as "Code" for medicinal products for human use, adopted by Italy with Legislative Decree no. 219 of April 24, 2006. Article 10, paragraph 5(b) of the Decree defines an equivalent (or generic) as "a product having the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference product has been demonstrated by appropriate bioavailability studies".
Bioequivalence between two drugs is the therapeutic equivalence between two essentially similar formulations containing the same active ingredient. Two products are bioequivalent when, with the same dose, their blood concentration profiles relative to time are so similar that they are unlikely to produce significant differences in efficacy and safety effects. Bioequivalence studies are, in essence, pharmacokinetic studies whose purpose is to compare the bioavailability of two products, i.e. the amount of drug that passes into the general bloodstream following administration, in relation to the speed with which the process occurs. The purpose of bioequivalence studies is to demonstrate that differences in bioavailability between two essentially similar products do not exceed a certain range of variation, deemed to be compatible with therapeutic equivalence.

[28]www.agenziafarmaco.gov.it/sites/default/files/medicinali_equivalenti-qualita_sicurezza_efficacia.pdf.

2.7.c Quality, safety and efficacy of equivalent medicines

In order to obtain the MA, an equivalent medicine must have the same quality requirements as the originator, and is therefore subject to the same tests as the reference medicines. The quality of a drug is obtained through a set of procedures set forth by Community law, the Good Manufacturing Practices (GMPs), implemented by the manufacturer from procurement of raw materials to release on the market[29].

GMPs contain provisions and provide for the relevant checks on the raw materials used in production, such as concentration, purity and stability of the active ingredient and of the excipients contained in the product. The checks, which must meet standards set at European level, also relate to all stages of production, including packaging, and are carried out through inspections at production sites. The inspections are conducted by AIFA if the national procedure is followed to authorise marketing of the product, or by the various EU member States (including Italy) if a Mutual Recognition (MR) or Decentralized (DC) procedure is followed. Many equivalents marketed in Italy were authorised through MR or DC procedures and then underwent the assessments and controls of several European regulatory agencies.

As to the safety profile, an equivalent can rely on the preclinical trials conducted for the reference medicinal product (and included in its authorisation dossier) and on the significantly reliable information contained in the package leaflet with regard to side effects. An equivalent drug can make use of the data collected during the many years of marketing of the reference drug (usually more than 10). This is why the clinical use of an equivalent is almost never associated with the onset of unknown adverse reactions, but tends to reproduce the same safety profile as the original medicinal product.

2.7.d Savings achievable with generics

Once the patent expires, the intellectual property rights held by the company on the invention or discovery of the substance lapse. After patent expiry, the law allows anyone with the appropriate technological equipment and facilities to reproduce, manufacture and sell a medicine whose effectiveness and safety are established and well known, subject to authorisation from AIFA. As a direct consequence of expiry of the patent on the active ingredient in its composition, the equivalent drug can be negotiated at a price at least 20% lower than brand-name medications. As mentioned above, a manufacturer requesting authorisation for an equivalent product can apply very competitive prices compared to the MA owner of the brand

[29] GMP principles are set out in the Commission's Directive 2003/94/EC of 8 October 2003, which lays down the principles and guidelines of good manufacturing practice with respect to medicinal products for human use and investigational medicinal products for human use. The directive was implemented in Italy by Legislative Decree no. 219 of 24 April 2006.

name product, because it does not have to invest resources in research (the active ingredient is known), or conduct preclinical and clinical studies to prove the efficacy and safety of the medicinal product in humans. Therefore, the introduction of an equivalent on the market is advantageous to the NHS as well, since the public funds saved on the reimbursement of generics can be used for innovative drugs that target chronic conditions of great social importance or rare diseases.

The data concerning drug consumption and expenditure in Italy reveal that in recent years increased entrance of expired patent drugs have been associated with significant cost savings. The impact of equivalent products on pharmaceutical expenditure is documented in particular by the decreasing trend in the prices of medicines reimbursed by the NHS and dispensed through pharmacies, which is reflected in the constantly decreasing trend of pharmaceutical expenditure under subsidised healthcare programmes, despite growing consumption.

The latest OsMed Report (2014) expanded the analysis on expired patent drugs, supplementing data from subsidized healthcare programmes with those relating to purchases by public health facilities, and is now able to provide a complete picture of the use of expired patent medicines in Italy, including at regional level.

From this combined analysis, it emerges that in 2014 the consumption of expired patent medicines accounted for 63.8% of drugs paid for by the NHS: specifically, 69.3% of consumption under subsidized healthcare programmes and 23.8% of the consumption of drugs purchased by public health facilities. In terms of spending, expired patent medicines accounted for 46.6% of the net subsidized expenditure, 2.8% of the expense for drugs purchased by public health facilities and 24.4% of overall public spending. The expenditure on expired patent medicines is more concentrated in the categories of drugs for cardiovascular and for gastrointestinal and metabolic disorders, where it accounts for 51.8% and 47.9% respectively of public spending in each category. Equivalents have accounted for 16.3% of net subsidized expenditure.

In the international ranking, Italy currently stands at third place after Greece and Ireland in terms of spending on drugs previously covered by patents; Germany, England and France are the countries with the highest rates of spending on generic drugs.

2.7.e Biosimilars: the new frontier of generics

An area of emerging importance within the context of expired patent drugs is that of biosimilars. The increasing use of biotech products results in growing costs for national health services. Biosimilars may provide a cheaper alternative compared to biologics that have lost their intellectual property rights. The availability of biosimilars promotes competition, potentially improving patient access to biologic medicinal products and contributing to the economic sustainability of health systems.

As biologics are complex products, the development and approval of corresponding biosimilars is a complicated and challenging process, which is conducted by regulatory agencies at the highest level of scientific assessment according to specific guidelines, constantly updated with the results from scientific and technological advances. Moreover, biologic medicinal products, including biosimilars, are essential for the treatment of a number of life-threatening diseases, for many of which in the past no effective treatment option was available.

AIFA has devoted and still devotes a great deal of attention to this subject, and in 2013, after a first public consultation, published a Position Paper[30] that focused on three fundamental aspects: definition and main criteria for characterization of biologics and biosimilars; understanding of the regulatory framework in force in the European Union, and role of biosimilars in the economic sustainability of the National Health Service.

A biological medicine is defined as "a medicine that contains one or more active substances made by or derived from a biological source. Some of them may be already present in the human body: examples include proteins such as insulin, growth hormone and erythropoietins. The active substances of biological medicines are larger and more complex than those of non-biological medicines. Only living organisms are able to reproduce such complexity" (EMA/837505/2011). The category of biologics includes pharmaceuticals based on active ingredients such as hormones and enzymes, blood products, immunoglobulins and allergens, or monoclonal antibodies and immunological products, such as serums and vaccines.

A biosimilar is a medicinal product that is similar to a reference biological product already authorised in the European Union, for which patent coverage has expired. The Position Paper shows that biosimilars, being obtained through different processing methods than those used for the reference products, are not identical, but essentially similar in terms of quality, safety and efficacy.

As mentioned above, the development and use of biosimilars provide a crucial opportunity to optimise the efficiency of healthcare systems and services, while having the potential to meet a growing demand for health, in terms of efficiency and personalisation of therapies as well as safety of use.

In terms of savings that can be generated, the role of biosimilars is not comparable to that of equivalents: 20-30% for biosimilars vs. 40-70% for generics. The differences are due to high production costs, absence of automatic replacement mechanisms, and delays in market entry as a results of litigations over intellectual property rights.

Nevertheless, the development of competition resulting from the introduction in the coming years of even a small number of high-expenditure, high consumption biosimilars will ensure

[30] Following requests for clarification received after the adoption of the Position Paper, the Agency found it appropriate to intervene again on the subject through the reopening of public consultation. The results, currently under evaluation by AIFA's Technical-Scientific Committee, will be made available shortly.

a reduction in healthcare costs and savings of several million euros per year, increasing the number of patients treated with the same budget, and will allow the funding of other treatments, stimulating innovation.

To date, 20 biosimilars have been authorised by EMA in the European Union through the centralised procedure (7 substances have been approved: somatropin; epoetin alpha and zeta; filgrastim; infliximab; follitropin alpha; glargine insulin).

As stated above, European and national regulations clarify that biological medicinal products and biosimilars cannot be treated as generic products, thus excluding automatic mutual substitution. The approach to substitution is not identical in Europe, in that decisions on interchangeability are the responsibility of individual member States, and different positions have been expressed by the regulatory agencies also in dedicated Position Papers (France, Netherlands, Finland). Unlike the European regulatory framework, the US legislation on biosimilars[31] has introduced, in addition to the concept of biosimilarity, the definition of interchangeability at the time of approval of the biosimilar product, providing for a specific authorisation procedure.

In Italy, available biosimilar products are currently excluded from the transparency lists that allow substitution between equivalent products. The choice to treat a patient with a biologic or biosimilar product is therefore a clinical decision that the physician is responsible for making in consultation with the patient. Biosimilars constitute treatment options that should be preferred, whenever they also offer an economic advantage, especially for the treatment of naïve patients (i.e. patients not exposed to previous treatments or for which, according to the physician's judgment, enough time has elapsed since the last treatment).

In Italy the use of biosimilars is still limited. However, in 2014 all biosimilars recorded an increase in consumption, especially for biosimilars of epoetins (+111.6% compared to 2013) and growth factors (+33.7%), which has allowed us to obtain reductions in spending (–11.0% of the expenditure for growth factors and-3.0% of epoetins compared to 2013).

As revealed by the indicators of appropriateness of use introduced in recent OsMed Reports, with reference for example to the use of erythropoietin to treat anaemia, in recent years there has been a significant increase in the percentage of patients who were administered the biosimilar product when starting a new course of therapy. In 2014, the percentage of patients who started a new course of treatment with biosimilar epoetin alpha was 55.9%, up by 54.6% over the previous year (in 2012 the same percentage was only 18.7%).

The prices of biosimilar products in Italy have been negotiated with reductions ranging from 15% to 28% of the price of the reference biological product.

[31] The FDA's "Purple Book" lists biological products, including any approved interchangeable biosimilars and biologics. Should they be defined as "interchangeable" by the FDA, biosimilar biological products can be dispensed in place of another biological product, because once they are recognised as interchangeable the pharmacist can replace one with the other without the need for the physician's prescription.

2.7.f Biosimilars: towards a common European vision

Among the initiatives aimed at defining the conditions required for informed use and adequate access of patients to biosimilar medicines, AIFA has played an active role within the *Market Access and Uptake of Biosimilars* workgroup, within the *Access to Medicines in Europe* platform established by the European Commission.
The group analyzed issues related to the improvement of information on the concept of biosimilar medicines and the scientific concepts and processes required for their approval; the conclusions that have been drawn are relevant to decision makers, scientific societies, healthcare providers and authorities, as well as to patients and patient organisations.
In order to provide adequate information on biosimilar medicines to the different categories of recipients, the workgroup, in close cooperation with the European Commission, has prepared a Consensus Paper ("What You Need to Know About Biosimilars") which includes a specific Q&A section and is addressed to patients, physicians and payers. AIFA contributed to the document and promoted its dissemination by posting an Italian translation on its institutional portal.
In summary, the following are the key messages contained in the document: a biosimilar is a biological medicine similar to another already authorised biological medicine (the "reference product"); the biosimilar medicine is expected to have the same safety and efficacy profile as the reference product and is approved for all the indications of the reference product or only for some of them (depending on individual cases); biosimilar medicines are produced according to the specific provisions of Community law, which include clearly defined high quality, safety and efficacy standards; the development and manufacturing process of biosimilars are more complex and expensive than those of generics obtained by chemical synthesis; the standards set by the European Union's Good Manufacturing Practices (GMPs) apply to the production of biosimilars as to that of any other biological product; compliance with the European Union's GMPs is verified through routine inspections carried out by the competent national regulatory authorities of EU countries.
In addition to participation in technical focus groups, workshops and information and training programmes for health providers, the Agency has given its contribution also by publishing in 2013 the article "Biosimilars: the paradox of sharing the same pharmacological action without full chemical identity" in the journal *Expert Opinion on Biological Therapy*[32]. The article points out that the use of biotechnological medicines is on the increase, resulting in higher costs for National Health Services (NHS), and that although biosimilars offer opportunities to improve access to care, the public may suspect receiving low-quality drugs for

[32] Authors: Pani L., Montilla S., Pimpinella G., Bertini Malgarini R.

the sole purpose of achieving monetary savings. The article emphasises the fact that no drug with lower pharmaceutical quality than the existing alternatives can be authorised on grounds of lower price, and that biosimilars can only be authorised if their quality is of the same level as that of the originator. It also clarifies that, with respect to chemical identity between the biosimilars and the originators, any differences in quality attributes should be justified and it has to be demonstrated that it does not produce any impact on the safety and efficacy of the biosimilar, based on the results of tests and scientific studies including non-clinical and/or clinical pre-authorisation studies. The biosimilar product's safety profile may be different from that of the originator, or change over time for the same product, whether reference or biosimilar. Because of these aspects, misgivings still persist and limit a more widespread use of biosimilars. These, however, can be overcome through initiatives to disseminate information about key biological issues related to biotech drugs and through the continuous updating of the regulations laid down by the regulatory authorities to evaluate biosimilarity and monitor post-marketing safety.

2.7.g The nomenclature of biosimilar medicines

One aspect that has given rise to international debate and controversy internationally, and which all the players involved (medical institutions, regulatory agencies, pharmaceutical companies and patient organisations) have been discussing for quite some time is the nomenclature of biosimilar medicines, which we shall only mention briefly in this document, recalling the initiatives undertaken in this regard by the World Health Organization (WHO) and the FDA.

The WHO, which is already in charge of generic drug naming according to the International *Non-proprietary Name* (INN), accepted the objections raised by some representatives of the regulatory agencies who expressed concerns on this issue (particularly because of the differences in approach between countries), and put forward a proposal for a new nomenclature for this product category.

The proposal is aimed at developing a unique identification code, called *Bilogical Qualifier* (BQ) to apply to all biological medicines, including biosimilars. The BQ code would consist of a four-letter suffix and, according to the developers of the model, would ensure sufficient flexibility in the near future allowing 160,000 four letter combinations. A specially created database would count all the codes issued. According to WHO, implementation of the BQ would put an end to the diverse naming system adopted by the different jurisdictions. A biological product can be sold under a different name depending on the country where it is registered. EMA, the FDA and the TGA (*Therapeutic Goods Administration*) will give a final opinion on this matter in the coming months.

Meanwhile, last September the FDA published in the United States draft guidelines intended for companies for the naming of biological products; according to these guidelines, manufacturers are required to include a non-proprietary name containing a four lowercase letter suffix designated by the Agency, essential to clearly identify the products and consequently to improve pharmacovigilance.

According to the FDA's proposal, the originator products and their corresponding biosimilars will share the name of the basic drug, followed by a single meaningless four letter suffix, so that the originators also contain a suffix, albeit different from that of the biosimilars. At the same time, the Agency is evaluating comments on whether a different suffix should be required for products considered interchangeable with the reference version.

The FDA specified that the current draft guidelines are designed, among other things, to prevent accidental substitution of non-interchangeable products and to facilitate control and monitoring of their use once placed on the market. The FDA is also considering the most appropriate approach with respect to previously approved biological products, which have non-proprietary names without a suffix. For this reason, the Agency is working on a bill to designate non-proprietary names that contain a suffix for the six previously approved biological products.

As these examples clearly show, the nomenclature of biosimilars is indeed a very sensitive matter. The naming of these products is a key issue to ensure their safe use and promote their acceptance.

3. The future of treatments, the treatments of the future

From gene therapy genetic editing, from medications that are 3D-printed directly from the patient to the development of immunotherapy, the pharmaceutical industry is increasingly becoming a crossroads of scientific and technological innovation. Confronted with this powerful and potentially unstoppable wave, regulators must maintain a scientific approach, analyse, establish rules and procedures, and finally evaluate. This is the great challenge of innovation: the ability to develop tools that will understand and measure its essence; to distinguish, among the chaotic mass of everything that is labelled as "innovative", the elements that bring real benefits to patients and medical science.

3.1 Genetic editing and "molecular cut and paste": new hopes for cures?

About fifteen years ago, the announcement to the world that the entire human genome had been sequenced raised huge expectations for the potential medical applications of the new knowledge, and in particular for the possible significant improvement of predictive, diagnostic and therapeutic capabilities of medical genetics.

Despite some hasty and overly optimistic forecasts and the occasional blunder, recent studies seem to promise a breakthrough approach to a number of diseases. In most cases these studies are still in the early trial stages, but some of them were tested in human already in 2015[33]. The gene therapy clinical trials conducted so far have mostly focused on cancer, cardiovascular disease and monogenic hereditary diseases. Conversely, gene therapy promises to find application in infectious, inflammatory, autoimmune and neurodegenerative disorders as well. Nearly all major pharmaceutical companies have announced the start of gene therapy trials, and the rebounds of some of their stocks on the NASDAQ in recent months may reflect investors' growing interest in this sector.

The main techniques used so far by researchers have been based on the insertion of a functioning gene into the DNA or the modification of an already present defective gene: therefore, the diseases that are most likely to be cured are those caused by a single mutation (as is often the case). Gene correction can take place ex vivo, i.e. a group of defective cells are extracted from the patient and treated *in vitro* before being reinfused, or *in vivo*, through corrections carried out using special carriers.

Targeted genome editing by artificial nucleases seems to be a promising strategy. This concept was introduced in 1990 with the development of artificial enzymes that cut the DNA, known as Zinc Finger Nucleases (ZFNs). ZFNs bind to a specific section of DNA and create a disruption at both ends: this is known as "molecular cut and paste". At this point, a specific laboratory-produced DNA sequence can be inserted. The cells will read the sequence again, this time starting from the correct complementary bases provided from the outside, until a healthy and functioning version of the gene is restored.

Sickle cell disease has proven to be an ideal candidate for research in this area[34]: it is caused by an amino acid mutation in a specific site of the hemoglobin β chain gene. The result is the production of abnormal hemoglobin proteins that bend the red blood cells, giving them the typical sickle shape.

[33] We quote by way of example some articles on gene therapy clinical trials in humans: http://pharmastar.it/index.html?cat=6&id=19566; http://www.quotidianosanita.it/scienza-e-farmaci/articolo.php?articolo_id=31016; http://www.huntingtonsociety.ca/human-trials-begin-on-gene-therapy-for-huntington-disease.

[34] Gammon K."Gene therapy: Editorial control", *Nature* 515, S11-S13, 13 November 2014.

The bent cells become sticky, adhere to each other and block blood vessels, preventing the passage of oxygenated blood.

Gene therapy has been used successfully in patients with immune system disorders, and sickle-cell disease is one of the next goals of researchers. The farthest advanced of these projects is now about to undergo clinical trial, and others will be following soon. The approaches being developed for the treatment of sickle cell anaemia are of both the types described above, i.e. conventional gene therapy, also known as "gene addition", and genetic editing. In both approaches, the modified DNA results in the formation of a normal functioning protein.

In sickle cell anaemia, the only cells that need DNA modifications are the haematopoietic stem cells found in the bone marrow. These cells continuously produce new red blood cells to replace the lost one. "In sickle-cell disease, the only cells that need their DNA edited are blood stem cells — also known as haematopoietic stem cells — which are found in bone marrow. These cells continually form new red blood cells to replace those that are lost, and reprogramming just a small fraction of them will create enough perfectly formed red blood cells to eliminate disease symptoms."

Although these approaches do look promising, several issues must be addressed before application in humans is attempted: for example, it must be made sure that the treatments hit their targets accurately and do not cause irreparable damage to the cells or introduce additional genetic information that could cause serious effects such as cancer.

Gene addition is about to become the first gene therapy tested in humans for sickle cell disease. At the Regenerative Medicine Research Center of the University of California, molecular physician Donald Kohn is developing protocols for a clinical trial of this technique; the trial began enrolling patients back in late 2014[35].

Researchers will collect bone marrow from the hip of patients with sickle cell disease, from which they will extract haematopoietic stem cells. Using a viral vector, they will introduce a new functional haemoglobin gene into the cells DNA; the old gene, though present, will be muted because the new one will take over. The modified cells are then reinfused into the patient's bloodstream and will migrate into the bone marrow, where they will provide a continuous source of healthy red blood cells.

According to Kohn, this approach has the potential to cure sickle cell anaemia with greatly reduced side effects compared to bone marrow transplant. He has tested the technique by injecting modified human haematopoietic stem cells in mice: two or three months later, he found that they were entirely free of sickle cells. "The limiting factor in mice," said Kohn, "is

[35] https://clinicaltrials.gov/ct2/show/NCT02247843?term=Stem+Cell+Gene+Therapy+for+Sickle+Cell+Disease&rank=1.

that they can only sustain human grafts for that long. In humans, the correction should last a lifetime, as long as 50 to 70 years"[36].

One of the challenges in the treatment of sickle cell disease with gene therapy is the need to extract bone marrow to retrieve haematopoietic stem cells. In most other diseases, patients can be given medications that facilitate passage from the bone marrow to the bloodstream, where they can be easily collected. In patients with sickle cell anaemia, instead, these drugs can trigger a sickle cell crisis, a painful event caused by damaged cells that aggregate and obstruct blood vessels. The crisis can be accompanied by anaemia, chest pain, difficulty breathing, thrombosis of the spleen or liver and risk of stroke. This is why researchers are force to collect bone marrow, a slow and difficult procedure that also limits the number of cells that can be harvested each time. According to Kohn is not yet certain whether this approach will provide a number of haematopoietic stem cells sufficient for reprogramming. Also, as with other bone marrow transplant procedures, the patient will still need to undergo chemotherapy to kill the remaining marrow cells, so as to allow the genetically engineered ones to survive once reintroduced into the body.

In parallel with this approach, Kohn is exploring the use of ZFNs to modify sickle-cell genes. He has already shown that approximately 7% of haematopoietic cells can be repaired by culturing using this technique and a viral vector. As the repaired cells continue to replicate, even this small percentage could be able to produce a sufficient amount of functional red blood cells. Kohn reports that patients showed significant improvements when only 10-20% of the cells of their donor's cells was successfully infused, and started producing healthy new cells. The advantage of gene editing over gene addition is that it provides a real correction. However, ZFNs are expensive and difficult to program. A gene modifying nuclease developed in 2010, called TALEN (transcription activator-like effector nuclease), uses a mechanism similar to ZFN but is less expensive and easier to work with. It was promptly adopted for use in sickle cell anaemia.

At the Salk Institute for Biological Studies, in La Jolla, California, stem cell biologist Juan Carlos Izpisua Belmonte uses TALEN with viral vectors called HDAdVs (helper dependent adenoviral vectors) to correct the sickle cell mutation. Instead of haematopoietic stem cells taken from bone marrow, Izpisua Belmonte's team collects cells that are easy to obtain, like blood, skin or fat cells, and transforms them into induced pluripotent stem cells (iPS), which can then be converted into any cell type. Researchers correct the haemoglobin gene defect *in vitro* using gene editing, then differentiate repaired iPS cells in blood stem cells. At this point, the repaired cells could simply be infused into the patient's bloodstream, from which they would enter the

[36] Romero, Z. et al. "β-globin gene transfer to human bone marrow for sickle cell disease", *J. Clin. Invest.*, 123, 3317-3330 (2013).

bone marrow and start producing healthy haematopoietic cells. Izpisua Belmonte, however, is also working on a treatment able to act inside the patient's body. His team is combining TALENs with the viral vector HDAdV to increase the success rate of gene editing, and is designing a plan to manage the hybrid vector directly in the bone marrow. Although each infusion can only correct 1% of cells, ten infusions over several months (i.e. a number that Izpisua Belmonte and his colleague Mo Li believe to be feasible in terms of time and costs) could alleviate symptoms of sickle cell disease. "Little by little, you are correcting the disease *in vivo*"[37] says Izpisua Belmonte. So far, this 'hybrid vector' technique has shown promising efficacy in umbilical-cord blood stem cells.

The latest tools available to the genetic editing technique are CRISPRs (clustered regularly interspaced short palindromic repeats[38]. While ZFN and TALEN use a protein that attaches to a specific DNA section, CRISPR use a "guiding RNA", which is much easier to program than TALEN and ZFN proteins and is also cheaper and more efficient. CRISPRs, which allow the performance of several genetic manipulations at a time, work in combination with Cas9 nuclease (CRISPR-Cas49): the CRISPR attaches to the target gene and Cas9 nuclease cuts both DNA strands, deactivating the gene. This approach was developed less than two years ago, but many researchers are investigating in parallel with other *in vitro* techniques. A recent trial has been successfully conducted in adult lab rats to treat type 1 hereditary thyrosinemia, a liver disease. The advantages of CRISPR over available technologies are evident. Compared to traditional gene therapy, which involves adding a functional copy of the gene, CRISPRs correct the gene defect at a deeper level by acting directly on the mutation and leaving no trace of the altered gene. The new gene, being located in its natural position within the genome, will thus be subject to the physiological control of the cell.

There are safety hurdles to be overcome before gene editing is used in humans, especially because it involves a permanent change in the genome. The thorniest issue is 'off-target' activity: for the technology to move forward, researchers need to better understand the effects of unintended changes to the genome away from the target gene. Gang Bao, a biomedical engineer at the Georgia Institute of Technology in Atlanta, is developing gene-editing strategies for sickle-cell disease and is paying particular attention to the challenge of limiting off-target effects: if erroneous cuts happen in a cancer-causing gene, they could potentially trigger tumour growth. Even a rate of off-target activity lower than 1% could still pose serious health risks. For this purpose, Bao's team created a software programme to predict where off-target effects could occur for the different gene editing techniques. The software predicted

[37] Gammon K."Gene therapy: Editorial control", *Nature* 515, S11-S13, 13 November 2014.

[38] Discovered in 1987 as an immune defence used by bacteria against virus invasion. It was not until 2012-2013 that its modifying potential was fully understood, when scientists revealed that it can be combined with a protein called Cas49 and used to modify the human genome.

114 potential off-target sites across the whole genome for the CRISPR/Cas9 system, and experiments confirmed 15 of them by sequencing the cleaved DNA.

Izpisua Belmonte's team is also looking at the rate of unwanted mutations caused by gene-editing techniques. The group created iPS cell lines and then edited half of the cells using HDAdVs and TALENs, but left the other half unedited. The edited cells had no more mutations than the unedited ones, indicating that — in contrast to Bao's findings for CRISPRs — the use of TALENs does not seem to make cells any less safe. Although human testing is still a few years off, they say that these results give them optimism about the potential for gene editing to work.

The other major challenge for gene-therapy researchers is ensuring that the edited stem cells survive and generate healthy red blood cells after they are reinserted into the bone marrow. Edited cells often die because of the amount of stress they undergo during therapy. Researchers might be able to improve the cell-survival rate by delivering other types of cells at the same time, and the speed of gene editing also seems to be important: the longer the cells are cultured *in vitro*, the less likely they are to survive. Based on his research so far, Bao thinks that CRISPRs are the best method for generating DNA breaks, but they are also more likely to cause off-target activity. TALENs are less efficient than CRISPRs, but they seem to have fewer off-target effects. The rate of off-target activity varies depending on the type of cells and the nuclease used. Kohn has compared ZFNs, TALENs and CRISPRs, and concluded that all three have therapeutic potential for patients with sickle-cell disease. Now the remaining challenges are delivering them to the target cell and accurately repairing the gene after the break. For sickle-cell gene therapy to become reality, the details must be sorted out on a large scale. Tinkering with human genes can yield both devastating and remarkable results, and the difference between the two often lies in a single nucleic acid of a single gene. This places a heavy responsibility on the shoulders of every researcher in the field, but the vast potential of gene therapy makes that burden worthwhile.

Gene editing promises significant results for the treatment of HIV as well[39]. The first case of HIV cure was already, in essence, a form of gene therapy. In 2007, a courageous patient was cured both of his acute myeloid leukemia and his HIV infection with a bone marrow transplant from a donor who was homozygous for a deletion in CCR5, the major cellular co-receptor used by HIV to infect CD4 T cells. With this transplant, the patient received an immune system that was impenetrable to the most common variants of HIV that use CCR5 to enter cells, R5-tropic virus.

This case generated enormous interest in gene therapy approaches to cure HIV by knocking

[39] Durand C.M, Siciliano R.F. "Dual zinc-finger nucleases block HIV infection", *Immunobiology*, January 2, 2014; Blood: 123 (1).

out CCR5 expression. One of the most promising methods to achieve this is the use of zinc-finger nucleases (ZFNs), i.e. engineered nucleases that target and cut specific cellular DNA sequences using an adenoviral vector delivery system.

Some strains of HIV have evolved to use a different cellular co-receptor, CXCR4. These X4-tropic viruses are rarely transmitted but develop within an infected individual over time, and are associated with a worse prognosis and rapid disease progression.

There is concern that the use of ZFNs that inactivate CCR5 (R5 ZFNs) will lead to the selection of X4-tropic HIV strains. As such, R5 ZFNs could not be used in individuals who harbor dual or mixed-tropic viruses, about half of individuals with AIDS. ZFNs specific for CXCR4 (X4 ZFNs) have been developed, but it was previously unclear whether they could be successfully used in conjunction with R5 ZFNs. To fully protect a cell from both R5- and X4-tropic viruses would require simultaneous editing of 4 alleles. In a recent study, published in *Blood*[40], Didigu et al provide convincing evidence that treatment with dual ZFNs achieves this goal, disrupting both CCR5 and CXCR4 within the same cell. Functional effects of the dual ZFN gene therapy treatment were further explored in a humanized mouse model of HIV infection.

A gene therapy approach that included the use of a R5 ZFN was found to be safe and tolerable in a phase 2 clinical trial, but it was not effective in reducing levels of HIV plasma virus. Low and transient engraftment of the genetically modified cells has been one of the problematic aspects. However, overcoming this limitation seems likely as the technology continues to advance. A more complex issue is that uncontrolled HIV replication seems to be required to select genetically modified cells. Interrupting antiretroviral treatment in HIV-infected individuals may be difficult to justify, given the growing evidence that delays and interruptions in therapy lead to clinical complications.

Finally, new findings suggest that gene therapy may not be necessary to HIV cure in the context of allogeneic stem cell transplantation. Maintaining antiretroviral therapy during transplant may be sufficient to protect donor cells from acquiring HIV. In parallel, donor haematopoietic cells should replace all host haematopoietic cells over time due to the allogeneic or graft-versus-host effect, which will non-specifically eradicate viral reservoirs.

Evidence supporting these hypotheses was provided by Henrich et al[41], who identified 2 HIV-infected individuals who had received allogeneic CCR5 wild-type stem cell transplants while maintaining antiretroviral therapy. Several years after transplant, the researchers did

[40] "Simultaneous zinc-finger nuclease editing of the HIV coreceptors *ccr5* and *cxcr4* protects CD4+T cells from HIV-1 infection", http://www.bloodjournal.org/content/123/1/61.

[41] "Long-Term Reduction in Peripheral Blood HIV Type 1 Reservoirs Following Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation", http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3636784/.

not detect HIV in the plasma or peripheral blood cells. Recently, antiretroviral therapy was carefully interrupted in these individuals, and rebound of HIV viremia has not been observed. Longer-term follow-up will be needed to determine whether these individuals are cured. What is clear is that research to find a cure for HIV and other diseases under investigation is rapidly evolving, and innovative strategies with multiple approaches will likely be required.
In a study published in the *Cell Stem Cell* journal[42], a team of Harvard researchers led by Derrick Rossi and Chad Cowan used the CRISPR-Cas-9 technique to modify the genes relevant to the fight against HIV, starting from cells originating from the patient himself: T-cells, haematopoietic stem cells and progenitor cells (HSPC), which are essentially the basis of the immune system.
The editing is accomplished through the removal of the main "gateway" used by the HIV virus to infiltrate the host cells, i.e. CCR5 receptor. The study authors report that use of single

[42] "Efficient Ablation of Genes in Human Hematopoietic Stem and Effector Cells using CRISPR/Cas9", http://www.sciencedirect.com/science/article/pii/S193459091400455X.

RNA guides led to highly efficient mutagenesis in HSPCs but not in T cells. A dual guide approach improved gene deletion efficacy in both cell types. HSPCs that had undergone genome editing with CRISPR/Cas9 retained multi-lineage potential. The researchers examined predicted on- and off-target mutations and observed low levels of off-target mutagenesis at only one site. According to the authors, these results demonstrate that CRISPR/Cas9 can efficiently ablate genes in HSPCs with minimal off-target mutagenesis. This result could find wide application in haematopoietic cell therapies, although it will take at least another five years before it can be tested in humans.

The proliferation of studies experimenting with gene corrections able to act on a number of diseases by restoring correct sequences and silencing altered or harmful genes, as we reported in the cases of sickle cell disease and HIV, leaves a wide margin to increasingly ambitious treatment targets, with undeniable ethical as well as financial implications.

Consider, for example, strategies aimed at fighting the causes of ageing. Gene therapy and the creation of new enzymes could help to act on natural cell repair mechanisms. Later we may be able to make use of futuristic technologies like nanobots[43], tiny devices that, by acting in a manner similar to our ribosomes, are said to be able to monitor the bloodstream, eliminating cancer cells and repairing the damage of the ageing process at molecular and cellular level.

Research studies conducted in this area in the next few years will tell us to what extent integrated sciences applied to medicine will be able to affect physiological and pathological states, revolutionising not only the concept of treatment but also the way we think of health and disease, and ultimately the very meaning of "human nature". For this revolution to take place, it will not be enough to simply develop enabling technologies, sophisticated as they may be; rather, we will need to investigate carefully how far we can push the limits of our inherent ability to change the world.

[43] Michio Kaku. *The Future of the Mind: The Scientific Quest to Understand, Enhance, and Empower the Mind*, 2014.

3.2 Biopharmaceutics on the technological and marketing cutting-edge of the pharmaceutical industry

The issue of biosimilars is one of the most controversial in the field of biopharmaceutical, and is particularly sensitive to Medicines Agencies worldwide which are trying to systematise the relevant regulatory processes through the adoption of guidelines, papers and official positions. This is the approach adopted by AIFA in its Position Paper on Biosimilars[44], which was made available at two subsequent times to public consultation by the interested parties, and by the European Medicines Agency (EMA), which has prepared and constantly updates a series of general and product-specific scientific guidelines[45] on these highly innovative new drugs. Even the US Food and Drug Administration (FDA) has recently made available a guide to biological drugs ("Purple Book"[46]) which includes biosimilars and interchangeable biological products. North American legislation has introduced the definition of interchangeability with the originator already at the time of approval, unlike Europe where such decisions are left to individual Member States. A biosimilar medicinal product was first approved in the United States in March 2015 (filgrastim-sndz[47]), approved for the same indications as the reference product. The FDA's Center for Drug Evaluation and Research received at least 17 new trial applications for biosimilar development programmes, including as many as 10 in 2013. It is worth pointing out that, at international level, Italy was one of the first countries to adopt a complex body of operating laws and regulations with regard to assessment and access to innovative medicines. In particular, the definition and assessment of innovation and the classification as innovative drug are procedures pertaining to AIFA (Agenzia Italiana del Farmaco – Italian Medicines Agency) and its technical-advisory Committees (in accordance with article 5, paragraph 2(a) of Law no. 222/2007). Using the therapeutic innovation algorithm and other tools, these bodies identify objective and transparent criteria to allow access to these products and negotiate a fair price. Sustainability of the healthcare system, in light of the introduction of increasingly innovative medicinal products, is a very sensitive issue for which it is essential to strike a balance between a fair return on the substantial investments made by companies and the right of universal and equitable access to care, which inspires the Italian NHS.

It takes about 7-8 years for a biosimilar to reach the market, at a cost ranging from 100 to 250 million dollars, probably more in the case of monoclonal antibodies. Gary Walsh, of the Department of Chemical and Environmental Sciences of the University of Limerick, Ireland,

[44] http://www.agenziafarmaco.gov.it/sites/default/files/AIFA_POSITION_PAPER_FARMACI_BIOSIMILARI.pdf.
[45] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c.
[46] http://www.agenziafarmaco.gov.it/it/node/16370/.
[47] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm.

has examined the European and US biopharmaceutical market from January 2010 to July 2014 and published the details of his analysis in an article in *Nature Biotechnology*[48]. "Thus far," he writes, "11 different biosimilar active ingredients have been approved within Europe: two somatropins (human growth hormones, hGH), two erythropoietins (EPOs), four filgrastims (G-CSFs), two follitropin alfas (follicle-stimulating hormones, FSHs) and, most recently, an antibody. By commercial agreement, several of these products are registered under two or more trade names, yielding a total of 19 products by trade name, with each having its own Marketing Authorization." Based on these figures, out of the total biosimilar products currently marketed globally (around 44), Europe is the largest market, followed by the United States and Japan[49].

In July 2014 the European Medicines Agency approved five applications for authorisation of biosimilars, relating to four different active ingredients. Significant among these are the approvals of the first FSH-based biosimilar and the first monoclonal antibodies that are biosimilar to Remicade (infliximab), and of Inflectra and Remsima (anti-TNF-α), biosimilar to Hospira and Celltrion, respectively. Last but not least, the European Commission approved the first advanced therapy product (entirely developed and manufactured in Italy) that uses autologous stem cells to treat corneal lesions caused by burns.

The European experience, writes the author, should mitigate commercial expectations in markets like the United States and Japan. After an initial spate, from 2006 to 2008, the rate of EU approvals underwent a noticeable slowdown. From January 2010 to July 2014, the EMA approved one in 2010, two in 2013 and one in 2014. The initial penetration was slow and total sales were limited, although recent data suggest that in 2013 total sales in key EU markets stood around 360 million dollars, with global sales exceeding US$ 676 million or 0.4% of the total biologics market. The investigation period also witnessed two withdrawals of biosimilars, *Filgrastim Ratiopharm* and *Valtropin*, both for commercial reasons, although neither had been actively introduced in the EU market after the initial approval.

A positive factor is that penetration in the European market for biosimilars finally seems to be firmly underway. By the end of 2012, biosimilar versions had gained in EU nearly 41% of the market of filgrastim and 19% of the market of short-acting EPO, from 30% and 15% respectively at the beginning of the year. Additionally, all biosimilars entered the market with an average discount of 30% compared to the reference products, and none presented unforeseen safety problems.

2012 saw the approval of the first gene therapy in Europe: the approval of Glybera (alipogene tiparvovec) in the Western world is a historical landmark for genetic-based drugs. This prod-

[48] Welsh G. "Biopharmaceutical benchmarks 2014", *Nature Biotechnology*, 32, 992-1000, October 2014.

[49] http://www.prnewswire.com/news-releases/biosimilar-market-growth-to-2021-driven-by-us-europe-and-japan-537998161.html.

uct's approval process was far from simple. The initial marketing application was filed in December 2009, and the EMA CHMP gave a negative opinion in June 2011 due to lack of sufficiently convincing data on long-term efficacy. The company appealed, but the CHMP confirmed at first the negative recommendation for approval. At the request of the European Commission in January 2012, the CHMP later reviewed the opinion, particularly for the case of a sub-cohort of patients with severe or multiple pancreatitis attacks, despite reduced dietary fats, and finally recommended the granting of a marketing authorisation in exceptional circumstances for this cohort, with the crucial contribution of the Italian representatives[50].

Considering that the approval of Glybera marks a watershed for gene therapy, we are unlikely, according to the author of this study, to see a flood of approvals for gene therapy products in the short to medium term. It remains to be seen whether the price of millions of dollars to be paid for Glybera is sustainable, given the reduction in health budgets. Moreover, no more than a handful of gene therapy products are in advanced stage (Phase 3) clinical trials. They are aimed at prostate cancer, myocardial ischemia and malignant melanoma.

Though chemically synthesized (not by recombinant DNA technology), antisense products have been historically included within the scope of biopharmaceuticals. At present, more than a dozen of these products have reached advanced stage clinical trials, although a blockbuster molecule has not yet been identified. The study period (January 2010-July 2014) saw the approval of *Kynamro* (mipomersen sodium), an "antisense oligonucleotide" (a very short DNA fragment intended to block the production of a protein called apolipoprotein B by attaching to the genetic material of the cells responsible for its production) for use in homozygous familial hypercholesterolemia.

Eleven of the 17 monoclonal antibodies approved during the study period contain a new active ingredient. Of these, three are particularly significant in terms of technological innovation. *Kadcyla* (trastuzumab emtansine), approved for treatment of HER2-positive metastatic breast cancer, and *Adcetris* (brentuximab vedotin), indicated for Hodgkin's lymphoma, have been approved as conjugated monoclonal antibodies and are available in Italy through the Registers of Monitored Drugs. *Gazyva* (US)/*Gazyvaro* (EU) (obinutuzumab) is the first glyco-engineered antibody.

Antibody-drug conjugates (ADC) are not new in themselves. *Mylotarg* (gemtuzumab ozogamicin), a prototype ADC, was approved in 2000 (despite its withdrawal from the market a decade later due to safety issues and despite its disappointing clinical efficacy). *Mylotarg* included a bacterial toxin (calicheamicin) conjugated with a humanized antibody and was indicated in the treatment of acute myeloid leukemia. In the following years, significant progress was made in this area, but technological innovations in the field of monoclonal antibodies

[50] http://www.agenziafarmaco.gov.it/it/node/11644/.

were not limited to ADC and glyco-engineering. Advances have also been made in Fc (crystallizable fragment) domain engineering, the development of bispecific antibodies, antibody fragment technology, as well as ongoing efforts to develop recombinant polyclonal antibodies. Two fragment antigen-binding (Fab) fragments, abciximab and ranibizumab, have been approved so far. The trend is to develop increasingly small antigen-binding fragments to facilitate their penetration into tissues and solid tumours. However, these fragments have some potential disadvantages, including short half-life. Therefore, their actual impact remains to be evaluated.

Although recombinant polyclonal antibody preparations are generally in an earlier development stage, they would provide several advantages over monoclonal antibodies, including the possibility to target different epitopes simultaneously on the same or on different antigens, thereby preventing the emergence of resistance in cancer and of infectious agents, and reducing the risk that the antigenic drift may make the antibodies ineffective.

Traditional blood-derived polyclonal preparations are characterized by heterogeneity and batch-to-batch variation, whereas recombinant-based polyclonal production could overcome these limits. With regard to delivery, Walsh notes that parenteral administration remains the main-stay of products approved during the current survey period, although one inhaled insulin product did obtain approval. Non-parenteral delivery routes offer potentially increased patient convenience and safety, although they are not likely to radically alter the course of treatments in the short to mid-term. Almost 12 billion injections are administered every year, with unsatisfactory delivery leading to over 20 million infections and over 100 million adverse reactions annually. Attempts to develop alternative delivery routes for therapeutic proteins are continuing, with the oral route viewed as particularly attractive.

As to future scenarios, according to Walsh it seems likely that approvals over the next few years will continue to be dominated by monoclonal antibody-based products and products synthesized using conventional expression systems and administered by means of conventional delivery. IMS Health projections suggest that biologic-based products will continue to gradually increase (from 18% in 2012 to 20% in 2017), with growth dominated by monoclonal antibodies and insulins. Cancer and infectious diseases will continue to be the target of most drugs under development.

Despite growing acceptance by the scientific community and the market, the commercial success of biosimilars, notes the author, is not yet guaranteed. The next wave will target multi-billion dollar blockbuster brands, quite a few of which have lost or will shortly lose patent protection, particularly from 2015 on. Biosimilar monoclonal antibodies (73 of which were under development in 2012, 9 having reached phase 3), will be particularly prominent, especially after the first such approval in the EU. The potential savings to healthcare systems due to price discounts afforded by biosimilar competition will be a strong commercial driver,

adds Walsh, especially in regions such as the United States, which accounts for about half of global biopharmaceutical sales, and where the average cost per day of a biological product is US$45 dollars, compared to US$ 2 for chemical small-molecule drugs.

The ongoing progress of research and innovation in the field of antibody engineering ensures that monoclonal antibody-based products will remain, in the near future, the most prominent class of biopharmaceuticals. In fact, the wide range of technological innovations will probably lead to a high level of competition. Only time will tell which technologies will underpin the most successful future wave of innovative products. Advances in the design and development of antibody-drug conjugates has stimulated renewed interest in this area, with over 30 products now in clinical development. Assuming satisfactory clinical performance, many of these are likely to reach the market, along with some promising antibody fragments.

In the area of regenerative medicine, several products based on tissue-extracted, fully differentiated cells have already led to the marketing of cultured autologous human chondrocytes with purified porcine-derived collagen.

Similarly, different types of stem cells and stem cell-derived therapies are also undergoing a development process, and at least six products are reaching phase 3 trials.

Overall, concludes the author, the survey period has witnessed some important milestones, including approval of the first biosimilar monoclonal antibody, the first gene therapy product and the first biological medicine of plant origin. The number of approvals and market value remains buoyant, and the current pipeline ensures that the biopharmaceutical segment will remain at the technological and commercial forefront of the pharmaceutical sector as a whole.

3.2.a Biopharmaceuticals. Approvals in Europe and the United States from 2010 to 2014

Monoclonal antibodies continue to establish themselves in the market, biobetters[51] are gaining ground, while the approval rate of biosimilars has slowed down significantly.

From 2010 to 2014 the approval rate of biopharmaceuticals in the United States and the European Union remained relatively steady compared with previous periods. 54 recombinant biologics were approved, bringing to 246 the total number of these products in the two markets. However, only 166 of these contain distinct active ingredients. Moreover, considering that 34 were withdrawn after approval, the number of biopharmaceutical products marketed in the United States and/or in the EU is down to 212. The number of annual approvals ranges from a low of 6 in 2011 to a high of 20 in 2013. Out of 54 biologics approved, 17 are mono-

[51] Biologics obtained from more innovative production processes than those of the reference drug, so that the biosimilar product has safety and effectiveness profiles that are even higher than those of the originator.

clonal antibodies, 9 are hormones, 8 are blood-related proteins, 6 are enzymes, 4 are vaccines, fusion proteins and granulocyte-colony stimulating factors, 1 was interferon and 1 was a gene therapy-based product. In terms of indications, the new approvals followed relatively predictable lines, with cancer representing the single most common indication (nine products), followed by inflammation-related disorders and haemophilia, metabolic disorders and diabetes, neutropenia and vaccines against infectious diseases.

Only 59% of the approved products (a total of 32) are truly innovative: of these, 30 contain different biopharmaceutical active ingredients, while *Eylea* and *Zaltrap* share their active ingredient (aflibercept), as do *Tresiba* and *Ryzodeg* (insulin degludec); the others are biosimilars, me-too products, or products already approved elsewhere.

The United States and the European Union recorded a similar number of approvals: 39 and 41 respectively. Over the same period, US regulatory authorities approved 147 pharmaceutical products containing new (bio)molecular entities. These numbers indicate that bio-pharmaceuticals account for about one quarter (26%) of all new medicines approved in the United States.

Compared with previous periods, Walsh observes, some interesting, albeit predictable trends emerge. After the first approval of a biopharmaceutical in 1982 (*Humulin*, recombinant human insulin), only 8 other drugs were introduced in the market in that decade. The number of approvals began to grow significantly in the 1990s, at almost constant rates in the two five-year periods. During the survey period there were 54 approvals, likely to be close to 60 before the end of the year.

The overall dominance of mAb approvals since the end of the 1990s continued into the second decade of the 21st century, with the increasing prevalence of human and humanised monoclonal antibodies over chimeric (particular murine) mAbs. Since the late 1980s, monoclonal antibodies have represented just over 10% of all approved biologic products, while between 2010 and April 2014 they represented almost 27%. The increase in the proportion of mAb-based products approved was constant over time, with one blip between 1995 and 1999.

As the probable effect on the market saturation in relation to demand, no recombinant thrombolytic agent, anticoagulant, interleukin or erythropoietin has been approved since 2010. Additionally, after an initial flurry of EU approvals for biosimilars in the 2006-2008 period, the approval rate has slowed down considerably. In contrast, the number of approved biobetters continued to grow. Examples include albumin fusions like *Eperzan* (a GLP-1 fusion) and the development of long-acting polyethylene glycol (PEG) derivatised proteins.

The market value of biopharmaceuticals has been constantly rising. In 2013, it reached a total sales value of US$140 billion, higher than the gross domestic product (GDP) of three quarters of the economies included in the World Bank GDP ranking (156 of the 214 coun-

tries). Data from various La Merie financial reports indicate cumulative sales that reached almost half a trillion dollars over the 2010-2013 period.

The single most lucrative product in 2013 was *Humira* (adalimumab), which generated global sales of US$ 11 billion, while a total of 37 individual biopharmaceuticals recorded blockbuster sales (>US$ 1 billion). *HUMIRA*, which was also the top selling biopharmaceutical in 2011-2012, generated US$ 35 billion in sales over the 2010-2013 period. The top ten taken together totalled sales of US$ 69.8 billion in 2013, representing 50% of total revenues from biopharmaceuticals in 2013. Monoclonal antibodies are the most profitable class of individual products. Total mAb sales (excluding Fc-fusion-based, antibody-like proteins, such as Enbrel (etanercept), reached US$ 63 billion last year (US$ 75.7 billion dollars including Fc fusion products). Moreover, monoclonal antibodies are 6 of the top 10 product sales in 2013 (seven including *Enbrel*).

In terms of therapeutic indications, most antibody and antibody-like products target inflammatory and/or autoimmune conditions (revenues of US$ 41 billion in 2013, with products targeting tumor necrosis factor [TNF], which alone generated US$ 30.5 billion) and cancer (revenues of US$ 26 billion in 2013, approximately 29% of the 2013 total global oncology market, estimated at US$ 91 billion). Among non-antibody-based products, insulins are the second most lucrative product class, with sales of US$ 21.5 billion in 2013, about 60% of the total global market for diabetes drugs.

Interestingly, only 1 of the top 20 biopharmaceuticals in sales was approved in the survey period (*Eylea*, number 20). In fact, 18 were approved a decade ago, and more than half (11 products) between the eighties and nineties. 40% of approved biologics are me-too drugs or biosimilars, while out of the 30 new products, 15 have orphan status. However, says Walsh, aggressive marketing and potential extended indications will probably result in at least some of these products becoming block-busters in the long run.

Another trend is the steady increase in the prominence of systems of mammalian over non-mammalian cell expression systems, in line with the ongoing increase in the proportion of molecules that harbour post-translational modifications, particularly glycosylation. Quantitatively, however, microbial production still prevails. Advisory firm BioProcess Technology Consultants (Woburn, MA, USA) estimates that the total biopharmaceutical manufacturing activity in 2010 amounted to approximately 26.4 tonnes of pure protein (active pharmaceutical ingredients), of which some 17.9 tonnes (68%) derived from microbial systems, and 8.5 tonnes (32%) from mammalian cell systems. Insulins constitute the majority of products produced in microbial systems, whereas monoclonal antibodies constitute the vast majority of medicines produced in mammalian systems. At a quantitative level, the trend is toward mammalian-based production, with demand for mAb-based expected to reach approximately 13.4 tonnes by 2016, nearly double the 2010 value.

Within mammalian expression platforms, Chinese hamster ovary (CHO) cell systems remain the most commonly used. A small number of products, mainly replacement enzymes with specific post-translational modification requirements, are produced in various human cell lines. Other mammalian-based production cells include mouse myeloma cell lines NSO and Sp2/0 and baby hamster kidney cells.
Although the use of *Escherichia coli* as an expression system continues to decline, it remains the single most common non-mammalian-based production cell type. Indeed, the only other bacterial systems currently in use are *Vibrio cholera* and *Bordetella pertussis*, each for the manufacture of single products: the former for *Dukoral* (cholera toxin subunit B) and the latter for *Triacelluvax* (recombinant pertussis toxin). Eukaryotic microbial expression systems based on yeast (*Saccharomyces cerevisiae* and *Pichia pastoris*) continue to be important and have remained common manufacturing systems.
Insect cell lines are used for three approved products: *Flublok* is a trivalent influenza vaccine based on haemagglutinin sequences of the three currently circulating flu strains produced in *Spodoptera frugiperda* (Sf) cells, using a baculovirus expression system. *Provenge* is a preparation of autologous peripheral blood mononuclear cells loaded with a recombinant fusion containing prostatic acid phosphatase and granulocyte-macrophage (GM)-CSF produced by baculovirus in Sf21 insect cells that are adapted to grow in serum-free media. *Cervarix* is a divalent human papilloma virus (HPV) vaccine, consisting of L1 proteins purified for HPV types 16 and 18, produced in a recombinant baculovirus expression system and the insect cell line Hi-5 Rix4446 derived from *Trichoplusia ni*.
In terms of transgenic animal production systems (which express recombinant products in their milk), rabbits have now joined goats as a means of biopharmaceutical production. *Ruconest* is a recombinant version of the human C1 esterase inhibitor (rhC1INH), produced in the milk of transgenic rabbits, and is the second transgenic animal-derived protein to be approved (the first from rabbits). In 2009, the FDA approved *Atryn*, a recombinant form of human antithrombin produced in the milk of transgenic goats using recombinant DNA technology.
Finally, 2012 also saw the first US approval of a biologic produced in plant cell culture: *Elelyso* (taliglucerase alfa) is a recombinant human glucocerebrosidase produced in cultured carrot root cells.

3.2.b What about Italy?

The 2015 Report on Biotechnologies in the pharmaceutical industry, edited by Farmindustria, shows encouraging figures with regard to the availability of *bio-tech* medicines in our country, and the same applies to the growth of Italian companies operating in this area.

145 products in various therapeutic areas are already present in Italy for the treatment of diseases, namely infectious diseases (71), oncology (27) and metabolic, hepatic and endocrine disorders (15). Of these products, 18 have orphan status, i.e. are medicines intended for the diagnosis, prevention or treatment of rare diseases or disorders, and mostly concern metabolic, hepatic and endocrine disorders as well as oncology. 303 projects are currently in various stages of Research and development, from basic studies, through which a new active ingredient is defined (41 projects in discovery), to large-scale therapeutic studies (109 phase 3 projects). An analysis of projects under development in Italy shows that 65% of these is at an advanced stage and will probably be available to patients in the near future.
Oncology is the therapeutic area with the largest number of R&D projects (130), most of which are in advanced stages of development (66.9% in phase 2 and 3). As highlighted in the Report, the biotech product pipeline focuses primarily on: monoclonal antibodies (33%), low molecular weight products (28%) and recombinant proteins (12%). 8 projects that have obtained orphan status from the EMA, 2 from the FDA and 36 from both, for a total of 46 recognised orphan drugs. The 199 biotech drug companies recorded 4.3% increases in sales revenues (7,302 million euros in 2013 vs 7,004 million in 2012), with a 3.3% growth in R&D investments (563 million euros in 2013 compared with 545 million in 2012), which in turn has allowed the number of people working on R&D projects to remain unchanged, with a slight increase of 0.4% (3,898 in 2013 from 3,881 in 2012), in counter-trend compared to national figures. From a geographic point of view, Lombardy is the Region with the largest number of biotech drug companies (90 entities), followed by Lazio (37) and Tuscany (26).
The efforts of biotech pharmaceuticals have produced excellent results and have provided answers to issues related to the country's economic environment, such as the difficulty of attracting investments. These values highlight the role of these companies, defining them as a specialised segment of the pharmaceutical industry that brings a significant contribution to the sector's growth in Italy.
However, factors that should not be underestimated include the role of the Position Paper adopted by AIFA and its close collaboration with the Regions, which have resulted in a growth in biosimilar consumption in 2014 and a consequent positive impact on public finances. Data from the OsMed Report[52] show an expenditure reduction of 11.0% compared to 2013 for growth factors and of 3% for epoetins. The use of biosimilars in hospitals is now emerging as one of the main strategies aimed at controlling pharmaceutical costs. To promote the use of these drugs, many Regions have issued binding Regulations laying out specific dispensing constraints, such as the reference to prescriber centres or the recommendation to always use biosimilars instead of the biologics originators in naïve patients.

[52] "Use of medicinal products in Italy. National Report. Year 2014" AIFA.

The measures in force have significantly increased: 34 new measures have been introduced in addition to the 9 in effect last year.

To sum up, biosimilar medicines are an essential tool for the development of a competitive market for biologic products. This is a prerequisite to pursue the sustainability of the health-care system and innovative therapies, while continuing to ensure safety and quality for patients as well as timely and consistent access to innovative drugs, albeit in a framework public expenditure rationalisation.

3.3 From artificial DNA, new hopes for science and regulatory policy

"If you read a book that was written with four letters, you're not going to be able to tell many interesting stories. If you're given more letters, you can invent new words, you can find new ways to use those words and you can probably tell more interesting stories."[53]. But if the story we are telling is the story of life, then those extra letters can rewrite it in forms and expressions that had not even been imaginable so far. The metaphor was originally suggested by Denis Malyshev, one of a team of biologists of the Scripps Research Institute Department of Chemistry in La Jolla, California, led by Floyd Romesberg, who has succeeded in building two artificial DNA bases that can be accommodated in a cell. The results of this work were published some time ago in *Nature* ("A semi-synthetic organism with an expanded genetic alphabet"), causing a sensation not only among scientists.

For billions of years, the history of life has been written with only 4 letters: A, T, C and G (adenine, thymine, cytosine and guanine), i.e. the nitrogenous bases that make up DNA nucleotides. In complementary DNA strands, guanine is always paired with cytosine and adenine with thymine, forming base pairs (G-C and A-T) that have essentially the same shape and steric hindrance. All known forms of life contain and transmit genetic information from generation to generation using the bases found in nucleic acids.

With the creation of a living cell that has two artificial DNA bases in its genome, the alphabet of life is now enriched with two new letters. Since life on Earth is biochemically stable, the possibility of alternative alphabets requires robust experimental evidence. This is precisely what happened in this study, which demonstrated how a pair of synthetic bases can replicate steadily in an *Escherichia Coli* bacterium.

"Shortly after the discovery of DNA," wrote Ross Thyer and Jared Ellefson, biologists at the University of Texas, in an editorial[54] published in *Nature* alongside the main study, "it was proposed that analogues of natural bases could form a third functional pair, but nearly 30 years passed before advances in organic synthesis and the development of methods for amplifying DNA gave scientists free reign to explore this hypothesis. In 1989, a base pair formed from isomers of guanine and cytosine was synthesized, and replication, transcription and even translation of DNA sequences incorporating this base pair were demonstrated *in vitro*. Then in 1995 came the surprising finding that hydrogen bonding between bases was not an absolute requirement for complementary binding, and could be replaced by steric compatibility (the fitting together of matching molecular shapes) and hydrophobic interactions. This culminated in the independent development of three highly orthogonal base pairs, each capable of *in vitro*

[53] http://www.nature.com/news/first-life-with-alien-dna-1.15179.

[54] Thyer R., Ellefson J."Synthetic biology: New letters for life's alphabet", *Nature* 509, 291-292, May 2014.

replication fidelity exceeding 99%. Malyshev *et al.* now describe the development of a bacterium capable of faithfully replicating a plasmid — a small, circular DNA molecule — containing the hydrophobic d5SICS:dNaM base pair, thus creating the first organism to harbour an engineered and expanded genetic alphabet."

"What we have now is a living cell that literally stores increased genetic information," says Romesberg. He and his team have identified a pair base compatible with the enzymes involved in copying and translating the DNA code. Working on test-tube reactions, they have succeeded in obtaining a pair of synthetic bases that can copy themselves and be transcribed into RNA.

The first challenge to creating this alien life, wrote Ewen Callaway in its editorial "First life with 'alien' DNA,"was to get cells to accept the foreign bases needed to maintain the molecule in DNA through repeated rounds of cell division, during which DNA is copied. The scientists achieved this by engineering an *Escherichia coli* bacterium. They created a plasmid containing a single pair of the foreign bases and inserted it into *Escherichia coli* cells. A single-celled alga (diatom) supplied nourishment to foreign nucleotides, and the plasmid was copied and passed on to dividing cells of the bacterium for almost a week. When the supply ran out, the bacteria replaced the foreign bases with natural ones.

The goal of several research groups is now to induce the cells to produce the new bases autonomously, without the need to import them from the outside. Romesberg's team is working on getting foreign DNA to encode proteins containing amino acids other than the 20 that make up nearly all natural proteins. Amino acids are encoded by chains of three DNA letters, so the addition of two foreign DNA "letters" would greatly increase the cells' ability to encode new amino acids.

"The next step,"according to Thyer and Ellefson, "will be to ensure long-term maintenance. Perhaps the biological mechanism used by Malyshev and colleagues in *Escherichia coli* will allow the body to adopt the artificial bases as part of its genetic alphabet without difficulty. If this were the case, scenarios that had so far been unimaginable would open up to human genetic engineering. But perhaps the ultimate application of these base pairs, conclude the two scientists, will be to add new codons (triplets of nucleotides that specify which amino acids are incorporated into proteins) to the genetic code through codon-transfer-RNA interactions. This would significantly expand the number of available codons that can be assigned new translational functions, such as encoding of non-standard amino acids, so that synthetic biologists would not have to recode the translational functions of existing codons through painstaking genome engineering. In other words, an expanded genetic alphabet will help build an expanded translational alphabet."

The work conducted by the American biologists has been received with great enthusiasm in scientific circles. Applications in medicine will not be immediate and require further research

developments. Potential applications could include, in the pharmacological field, the incorporation into a protein of an amino acid able to recognise and kill cancer cells only; or, in the diagnostic field, the development of fluorescent amino acids that could help scientists monitor specific biological reactions under a microscope. New scenarios worth exploring and new challenges for science and regulatory policy.

4. The ethical and regulatory outlook in the Big Data era

The world of Big Data, masses of information made up of huge quantities of data sets of various types that cannot be managed with traditional databases and must be processed in real time, is fast becoming a feature in the field of research and development of new pharmaceuticals and, considering the quantity of data and the numerous opportunities for cross-checking, its management goes far beyond the national, and even the European level and must necessarily be dealt with globally. The analysis of increasingly significant quantities of data is broadening the spectrum of the possible, including in the health and pharmaceutical field. By collecting and analysing data, it is possible, for example, to more accurately define illnesses and implement surveillance to promote the identification of new public health responses and measures or enable comparative analyses between two pharmaceuticals using methods and schedules that before had been unthinkable. The world of Big Data, still largely to be discovered, is one in which the activity of the regulatory Agencies is vital to ensure compliance with the caveats connected to the purposes for which sensitive information is used and respect for privacy.

4.1 The Big Data revolution in the world of medicine

Technological and biomedical progress has produced a large volume of biological and health data undergoing rapid and continuous growth, generating a solid knowledge base that is potentially able to improve health services, thanks to more effective and personalised approaches in the prevention, diagnosis and treatment of illnesses and the possibility of making the distribution of health services more efficient, at the same time supporting innovation and economic growth.

The world of Big Data is featuring more and more in the field of research and development of new medicines and, considering the quantity of data and the numerous opportunities for cross-checking, its management goes far beyond the national, and even the European level and must necessarily be dealt with globally.

Big Data in pharmacology means large collections of information closely linked to the populations that take medicines, such as biometric data (height, weight, pressure, body fat etc.), data concerning the habits of the populations, uniform data on the objectives that are sought from the therapy, including data on side effects, reference data on the natural progress of diseases and data on the duration of the pharmacological response over time. A number of other biological variables, including geographical, are important to establish the effects of medicines and, equally, knowing whether the effect of a medicine can be influenced by non-biological variables in the populations carries significant weight, just as certain lifestyles can actually alter the efficacy of a medicine or modify its safety profile.

The analysis of these data is a complex and costly process that can provide an unequalled quantity of information that should be assessed, selected and arranged in hierarchies.

By collecting and analysing health data, it is therefore possible to define illnesses more accurately and implement surveillance that could promote the identification of new public health responses and measures. So-called "digital epidemiology" refers to a new generation of supervisory systems of social health that operate across international borders and supplement traditional systems, making use of access to the internet and the explosive growth in mobile devices and shared on-line platforms that continually generate large quantities of data containing information on health. By using global data in real time, digital epidemiology promises, for example, the speedy detection of the outbreak of an illness. The most recent case was the Ebola epidemic in West Africa in 2014.

The first evidence of the emerging outbreak was detected by digital surveillance channels, some time before the official reports. Moreover, the information gathered from various data sources can be used for epidemiological purposes that go beyond early diagnosis of the outbreak of a disease, such as, for example, the assessment of people's behaviour and attitudes to health and pharmacovigilance.

The latest DNA sequencing techniques offer powerful tools for identifying cases of illnesses, aiding diagnosis, providing responses to treatments and determining the best care for patients. For example, the mapping of the genome on a large scale, currently at significantly high costs, will, in the near future, provide health operators with an excellent aid for identifying personalised treatment, adapted to each individual patient, thereby improving the prescriptive appropriateness. Precision medicine, therefore, that takes charge of the patient throughout the care process, considering their specificity and uniqueness, through ways of intervening that are appropriate only for their situation, including from the perspective of increasingly effective prevention.

The genetic sequencing data is completely reliable in expressing increased risk factors but the predictive nature of DNA interpretation can only be balanced if genetics is combined with key epidemiological information. And this is where Big Data comes into play: being able to take into account the data of millions of individuals on the impact of a medicine or any adverse reactions is, indeed, a solid basis on which to subsequently interpret the human genome with the aim of creating personalised treatment plans.

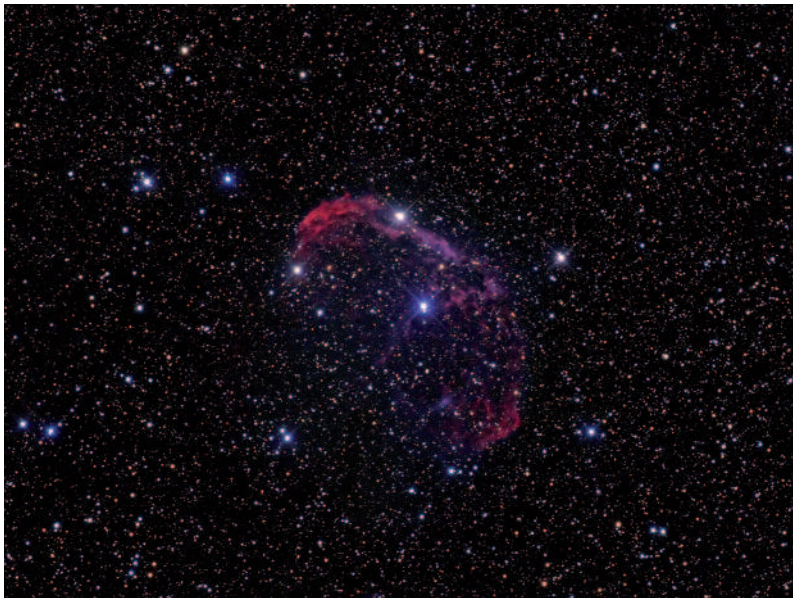
In the scientific field, therefore, Big Data can be an enormous resource but they can solve problems only when there is a proper experimental design, appropriate controls and the right questions. The field of Big Data requires, at all stages of the process, the use of much more sophisticated tools than traditional ones. While, on the one hand, it is true that artificial and human intelligence must complement each other in order to convert data to information and information to knowledge (which cannot be taken for granted) based on which decisions of a universal nature can be taken, on the other hand, the cooperation between human intelligence, which, at least in the short term, cannot be imitated by computer programmes, is the characteristic that makes the human species unique and that will also bring innovation in the development of pharmaceuticals in the years to come.

4.2 The infosphere and innovation in the pharmaceutical world

Imagine a future in which the identification of a molecule with a high probability of become a medicine is based on the use of predictive models that, by cross-checking enormous masses of clinical and molecular data, are able to predict with great accuracy the action mechanism of the active ingredient on the biological targets. Until recently, we would have catalogued this scenario under the heading "science fiction", but we now know that the so-called infosphere, that is, the semantic space made up of a collection of data, information and documents, is the present and future of innovation in every sphere of human activity, including pharmaceuticals.

The emergence on the market of tools for the analysis of digital databases is making it increasingly easy to manage projects that involve, simultaneously, different areas of the world, as usually occurs with projects connected to the development of new medicines. The management of great masses of data in the pharmaceutical world is, by definition, international and it is not enough only to look to the European level. The infosphere also comes into play in forming the inclusion criteria of patients in clinical trials, including new factors, such as genetic information, in the definition of populations. The launch on the global market of a medicine is implemented simultaneously throughout the world and it is very important to determine, for the populations under study, the more or less common characteristics in the responses, including with regard to the side effects. It is incredibly costly in terms of data analysis, because to analyse data so complex is, in turn, a complex operation.

The Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA) was among the first to put the accent on the central problem of interpreting the data, due to the fact that, because analysis of this magnitude returns a series of information, it must be graded in a hierarchy in order to establish which information is of most value.



The potential of Big Data is only one side of the coin, the extensive use of personal information implies ethical and legal questions that cannot be ignored.

The people who take part in the research can give consent to the use of their data at a certain time, for example

today, but the use that will be made of that data in ten or twenty years may be completely different.

With regards to the ownership of the data, there are two distinctly contrasting views. Some companies claim that the data belong to them because they produced them, however some regulatory agencies, such as the AIFA, believe they should be made public.

But the future will not be the exclusive prerogative of technology, indeed, the ability to cooperate is where human brains excel, producing peaks of functionality and beauty that no machine can equal. According to the AIFA, therefore, the use of around 2 exabytes (equal to two million gigabytes) of data, produced every year and stored in databases and Clouds throughout the world, will still be governed by tools designed by millennia of human evolution. There are 10,000 to 50,000 synapses for every neuron in the human brain and so, putting the overall number of contacts together, we obtain a number for every brain greater than the number of all the visible stars in the firmament.

These numbers should give us pause for thought.

4.3 Patients, Digital Health and IoT (Internet of Things)

"The World is the totality of facts, not things"

Ludwig Wittgenstein cannot be contradicted, he is indubitably perfectly correct. In the meantime, however, while we try to construct a logic that precisely describes the facts that make up the world around us, we are starting to analyse what we have online.

The Internet of Things, or the IoT, is a collection of processes that establish increasingly close relations and interconnections between the digital infrastructure and the objects we use every day, if furnished with identification (for example, IP numbers or DOI = Digital Object Identifier). For visionaries, the IoT is a future that divides, as often happens in these cases, the "apocalyptic" on one side from the "integrated" on the other.

Whatever position is adopted, it is clear that the IoT will be one of the most important economic drivers in the years to come. A study by *Accenture* estimated that, between now and 2020, the intelligent dialogue between system platforms, applications and objects, that is, the industrial *Internet of Things*, will bring added value to the global economy that can be quantified at around 14 trillion dollars.

Beyond the economic-financial aspects of this new industrial revolution, there are also technological-social components underway in the field of health that are interesting for a regulatory agency like the AIFA. The penetration of the social media and mobile technology is changing the expectations and the prerogatives of the citizen-patient, increasingly at the centre of health care. According to Eric Topol, a doctor and editorial director of *Medscape*, "We are embarking on a time when each individual will have all their own medical data and the computing power to process it [...] this will set up a tectonic (or "tech-tonic") power shift, putting the individual at center stage. [...] What have been dubbed the six most powerful words in the English language – "The doctor will see you now" – will no longer be true."[55]

Some, in the health and pharmaceutical world, have begun to become aware of this change and there are numerous initiatives that aim to make use the potential of the IoT to create new value for patients and for society overall. All this comes under the term digital Health (NOT Healthcare), from the English *Mobile Health* (mHealth), which refers to "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices."[56]

[55] https://www.elsevier.com/connect/Dr-Eric-Topol-Digital-healthcare-will-put-the-patient-in-charge.

[56] World Health Organisation "mHealth – New horizons for health through mobile technologies, Global Observatory for eHealth series", Vol. 3, pag. 6.

These are innovative ways for collecting useful data for more accurate diagnoses and responses to treatments (efficacious and/or safe) in real time because the patient agrees to be permanently connected with the aim, amongst others, of enabling us to find out how his/her daily life influences actual clinical practice.

The patient, in turn, can access personalised data at any time on their clinical and physical characteristics, lifestyle, the conditions of the local environment, immediately receiving the benefits of active and responsible participation in their own care or maintenance of their state of health, the so-called *patient digital empowerment*. This must be how more than 11,000 volunteers thought about it when, immediately after the presentation by Tim Cook, CEO of Apple, they signed up for his Research Kits, in 24 hours smashing all recruitments records of all time and all the worldwide clinical centres put together. Let us, therefore, examine the sacrosanct principle of privacy that we mean to defend but without ignoring these simple data that show that there are millions of individuals in the world (probably digital natives) belonging to social networks who are willing to put any personal data on the internet (just look at what is published in certain Facebook profiles).

Theses sources feed in petabytes of Big Data (it is estimated that, within the next decade, the data from personal sensors will rise from 10% to 90% of all stored information[57]), calling into question the concept of transparency and, it is worth repeating, with respect for the privacy of users, the availability of connectivity, the reuse of solutions and the interoperability of systems. Structural and policy changes that cannot be disregarded, moreover, by a robust legislative system (which we do not currently have), especially to protect the personal information that wearable sensors, new Apps and *Clouds' data up-and-down-links* make available, with potentially unlimited online accesses in terms of space and time. It is sufficient to realise that, so far, nearly 100,000 applications have been developed for mobile devices that involve managing human health in a global way and in a global market[58] and that many of them can put patients (their families and the entire healthcare network) in a position to request/make remote assessments of their physical condition.

In this regard, certification is more urgent than ever of the reliability and credibility of the content of all these Apps, especially those able to turn any mobile device into a real mobile doctor.

Some doubts remain about the real added value that these solutions can offer patients and doctors: many of the Apps on wellbeing, nutrition and lifestyle are limited to simply sending information, and these make up 70% of the total.

The irreplaceable role of the health care provider, to whom 30% of applications are aimed (around 30,000!), should enable the adoption of new ways of mobile working to take care of

[57] Pentland. A. et al. Improving Public Health and Medicine by use of Reality Mining, Robert Wood Johnson Foundation, 2009.

[58] Research2Guidance (2013), "The mobile health global market report 2013-2017: the commercialisation of mHealth apps" (Vol. 3).

the patient remotely, increasing, for example, adherence and data collection in a continuous and proactive way.

According to the AIFA, this type of research should be incentivised, and web Health business should be supported, so that really innovative applications can be developed. In the United States, for example, traditional companies and start-ups are investing in the sector of sensors for vital signs and the so-called activity trackers, generating a market share that, according to Frost&Sullivan[59], will reach 800 million dollars in 2020.

"[...] The Internet will disappear. There will be so many IP addresses... so many devices, sensors, things that you are wearing, things that you are interacting with that you won't even sense it. It will be part of your presence all the time. Imagine you walk into a room, and the room is dynamic. And with your permission and all of that, you are interacting with the things going on in the room."[60]

This accurate description of the near future, which contains a rather bold forecast about the destiny of the Internet, would have no value had it not been formulated by an expert in the digital world: Eric Schmidt, CEO of Google.

The same challenges are now facing Europe and Italy: as laid down by the recent Digital Healthcare Pact, remote monitoring will be one of the levers for reducing hospitalisation costs and, at the same time, improving the lives of the chronically sick and an ageing population, encouraging more effective prevention.

When this global revolution arrives, because there is no doubt it will arrive, will we be ready?

[59] Frost & Sullivan. *Wearable Electronics Enabled by Sensors*, February, 2015

[60] Google Chairman, "The Internet Will Disappear", see also: http://www.hollywoodreporter.com/news/google-chairman-eric-schmidt-internet-765989.

4.4 Open Data and the international debate

Open Data are digital data made available in a way they can be technically and legally used, freely distributable by everyone in every way, time and place[61]. One of the most significant current initiatives in this field, the third "International Open Data conference" (held in Ottawa, Canada, in May 2015)[62], was an opportunity for the analysis, study and comparison of the models and policies adopted by various countries on the release and dissemination of open data.

During the meeting, an exercise in online participation was launched that led to the drawing up of an agreed, definitive text, the *Open Data Charter*, approved on the sidelines of the General Assembly of the United Nations on October 2, 2015.

The international Open Data Charter is a document that came about on the initiative of the United States, Japan, Germany, France, United Kingdom, Canada, Italy and Russia in 2013, with the aim of bringing the issue of open data to the centre of international debate and involving the governments of signatory nations in the adoption of effective measures to support the release, dissemination and reuse of "liberated" data. As part of the third International Open Data Conference, various subjects, including governments and associations, defined a new version of the charter, subjecting it to online consultation, which was completed in August 2015.

All the speeches and remarks, around 350, contributed to the drawing up of the final document, which can currently be found on the website of the *International Open Data Charter*.

Basically, the charter is based on six cardinal principles and on certain rules intended to encourage the accessibility, comparability and completeness of open data at the global level. Theses rules also aim to promote the dissemination of the culture of open data both as a guide for sustainable development and as a powerful tool for transparency, the battle against corruption and social control.

Members of the Open Data Charter, moreover, intend to collaborate in ensuring the Charter is also adopted in countries not involved in drawing it up and, above all, in the creation of standardised packets of freely usable data, in addition to the great undertaking of the adoption and promotion process of the document.

Specifically, the Charter consists of a preamble and six cardinal principles, based on access to and reuse of data.

The preamble forcefully states the concept whereby open data are at the centre of global change and are fundamental in attaining the objectives of a more equitable society and one that promotes collaboration with citizens. Open Data represents not only an opportunity to be

[61] Internation Charter of Open Data http://opendatacharter.net/wp-content/uploads/2015/10/opendatacharter-charter_F.pdf.
[62] Open Data Conference: http://opendatacon.org/.

seized, but also a collective resource, an effective public control of the government's activities, an instrument of innovation able to generate economic and social benefits.

We now look in detail at the cardinal principles, that is:

- Open by default data
- Timely and Comprehensive data
- Accessible and Usable data
- Comparable and Interoperable data
- Data For Improved Governance and Citizen Engagement
- Data For Inclusive Development and Innovation

In the first, *Open by default*, it should be made clear that data must be open as a matter of principle, with the only constraint being the protection of privacy, and that it is necessary to promote the development and adoption of resources for the creation, use and exchange of data. In this regard, precise legislative measures were promulgated, accompanied by an awareness and training programme that promotes open culture.
The second, *Timely and Comprehensive*, underlines that the data must be complete, accurate, timely and high quality. Users are encouraged to provide adequate feedback to ensure both constant quality and the implementation of any corrective actions.
The third, *Accessible and Usable*, recognises that data can contribute to improving the decision-making processes of governments, organisations and associations. For this reason, they must be accessible, easy to identify and released without any bureaucratic or administrative barriers and, what's more, under a non-restrictive licence.
The fourth, *Comparable and Interoperable*, makes clear the data must be easy to compare with different sectors, in different geographical areas and at different times. Structured and standardised training is therefore necessary to ensure interoperability, traceability and effective reuse. Users must also clearly understand the source, the strong and weak points and the analytical limits of the data.
The fifth, *For Improved Governance and Citizen Engagement*, demonstrates how the release of open data would strengthen governance and the faith of the citizens in the institutions, in addition to providing a useful tool for improving the decision-making processes. It is fundamental that the data concerning transparency or corruption are open and that information is regularly released on the state of progress of the initiatives on releasing open data.
Finally, in the sixth and last, *For Inclusive Development and Innovation*, the importance is recognised of the openness of the data in stimulating creativity, innovation and sustainable development. The role of governments is not limited, however, to the release of open data but

also in playing an active role in the effective and innovative use of Open Data, ensuring that all stakeholders have the tools and resources to understand and use the data effectively.
Italy, which took part in drawing up the document with AgID, officially signed up to the Charter on October 20th of last year, in the course of the OGP Global Summit held in Mexico City, but the legislature had, in recent years, already sought to clarify that the data is not only the heritage of citizens, but also a tool of innovation and participation.
The principle of *Open by default*, indeed, is included in the Digital Administration Code and Legislative Decree 33/2013 and subsequent regulatory interventions have sought to reinforce the course embarked upon.
Since 2012, the AIFA has also dedicated a section of its portal entirely to the release of information and open data, both on its administrative activities and those connected to transparency, the culture of legality and anti-corruption.
In the Open Data section of the AIFA portal[63], there are 46 data sets, divided by area (Organisation and Personnel, Italian Medicines Agency Provisions, Appointments and Consultancy, Grants, contributions, aid, economic benefits, Calls for Tender and Contracts, Lists of Medicines, Pharmacovigilance, Authorised factories) and data are published on the personnel and collaboration, calls for tender and bids, the lists of transparency on equivalent medicines, the lists of active substances, the lists of deficient medicines, those responsible for pharmacovigilance and a variety of other content. These data are also included in the national catalogue of open data released by the Public Administrations.
The data distribution licence used by the AIFA is the CC-BY (attribution), version 4.0: this licence permits third parties to distribute, modify, optimise and use the data, including commercially, with the obligation to cite the source. Published personal data can be reused only under the conditions laid down by the current regulations on the reuse of public data (Community Directive 2003/98/EC, implemented by Legislative Decree 36/2006) in ways that are compatible with the purposes for which they were collected and recorded, and in compliance with the regulations on matters of the protection of personal data.
Open Data therefore are a guarantee of transparency and participation but also an important, effective instrument for protecting public health. The AIFA will continue to constantly monitor the initiatives of the Italian and international panorama on transparency, privacy and right of access.

[63] http://www.agenziafarmaco.gov.it/it/content/open-data.

4.5 "Giving meaning to data on health". From a comment in *Nature*, reflections on digital Healthcare

Never before have scientists, regulators and public decision-makers had tools and sources able to generate and make publicly available such a huge mass of data and information on health. It is a widely held conviction that the capacity to "give meaning" to these data will depend on the correct definition of the guidelines for research, regulatory assessments and healthcare policies.

This stimulating and compelling challenge is based on a convergence of interests, expertise and professionalism that can produce benefits for health and healthcare systems, but also for the progress of knowledge and economic development. Nevertheless, to ensure the hoped-for outcomes, it will be necessary to be committed to overcoming the current limits in the generation, analysis and interpretation of the data and in the application of the knowledge gained. Specifically, the reference is to the legal, ethical and deontological aspects and the dissemination of individual healthcare data; to the possibility of correctly assessing their relevance and quality and comparing and supplementing the data produced by multiple sources and originating from different databases; to the willingness of all the parties involved in providing a suitable, active contribution, also investing in training.

The AIFA has placed much stress on digitising its databases (for example, consideration is being given to the Monitoring Registers and the National Pharmacovigilance Network) and on the development of the skills in HTA and digital Healthcare, in the conviction that the regulatory evidence coming from uniform, certified data on the use of medicines can give direction to the increasingly complex decision-making processes on health matters.

From this perspective, the international debate on the prospects and limits in the management and exploitation of large quantities of healthcare data is of great interest. In a recent comment in *Nature*, Julian H. Elliott (senior research fellow of the Australasian Cochrane Centre at the University of Monash, and clinical research manager at the Infective Diseases Unit of the Alfred Hospital of Melbourne), Jeremy Grimshaw (senior scientists at Ottawa Hospital Research Institute and professor of medicine at the University of Ottawa) and colleagues underline the need to develop a "science of data synthesis" able to connect the enormous variety of information on health.

"We can sequence our entire genome and those of our bacteria, viruses and tumours. In principle, every visit to the doctor can be tracked from electronic medical records. Information on physiology, behaviours, diets, movements and interactions with others can be extracted from wearable devices, smartphone apps and social-networking sites. And thanks to the open-access movement and a shift in data-sharing norms, more data are being made publicly available. Yet" write Elliot and Grimshaw, "sifting through the information to find answers to ques-

tions about health is becoming increasingly difficult, even for the experts. The data exist in disparate domains, are generated using different methods, and are stored in different infrastructures — from the private servers of hospitals to global platforms, such as dbGaP, an open database of genotypes and clinical information."

Elliot and Grimshaw dwell on three aspects: data sharing, the management of bias and the connection of information. "We believe," they write, "that to consolidate data from different sources into comprehensive and coherent bodies of evidence on which decision-makers can act, researchers need to better exploit current methods and tools for data synthesis — and to develop superior ones."

Combining data or information from different sources or types of studies can provide deeper understanding of a phenomenon, such as in the case of Cisapride (a medicine for gastroesophageal reflux, since withdrawn from the market) authorised in the United States in 1993 on the basis of the data collected in clinical trials over more than ten years. "The drug's association with fatal heart-rhythm disturbances" recall the authors, "was understood only when data from clinical trials were consolidated with those from large, long-term cohort studies, which recorded Cisapride's effects in thousands of people."

"Likewise," they add, "the picture obtained from conventional influenza surveillance (which involves collecting data from primary-care clinics) can lag behind what is actually happening on the ground. Google collects real-time information based on the use of search terms related to flu symptoms, but these findings can be inaccurate. The best insights almost certainly come from aggregating these different data types."

"Formal methods for "evidence synthesis", write Elliot and Grimshaw, "were first developed in the social sciences in the 1970s. The techniques have since been adapted in many branches of science, and they underpin high-impact decision-making, for example in drug licensing. They generally involve identifying and collating all the available and relevant data; assessing each data source's strengths and vulnerability to bias; and deciding how to handle the different sources of data depending on their rigour and the question being asked (some data may be excluded, for instance). Then, if appropriate, a meta-analysis or qualitative assessment can be conducted, incorporating the information."

"Many researchers" the authors say, "immersed in the combination and analysis of large data sets that are vulnerable to spurious correlations, such as genomic or electronic-medical-record data, are unaware of evidence-synthesis tools and their potential usefulness. Conversely, many experts in evidence synthesis are unfamiliar with the methods often used to analyse large data sets relevant to health." These differences should therefore be combined and integrated.

Another question concerns the management of bias. "Scientists need to grasp the risks of bias associated with each data type and incorporate such risks into their analyses. For clinical

trials and observational studies of the effects of interventions, analysts can use the *Cochrane Risk of Bias* approach. Similar methods are needed to enable the detection and reduction of bias in other data types, such as social-networking and mobile-phone data. Methods to deal with bias must be incorporated into new analytical systems developed to guide decision-making in health care — including those based on natural-language processing and machine learning."

"In the short to medium term," the authors suggest, "funding programmes and a restructuring of departments in universities and institutes will be crucial to support collaborations between computational biologists, computer scientists, clinical and population-health researchers and specialists in evidence synthesis.In the long term, a new type of analyst, adept at appraising and combining diverse data types appropriately, may emerge."

But what could these changes lead to in practice? "One of the aims of the US Precision Medicine Initiative (PMI)," write Elliott and Grimshaw, "is to prevent people from getting cancer. This means understanding the effects of myriad genomic, behavioural and environmental factors and their interactions. The value of the Initiative will be enhanced if data from these very different domains can be combined appropriately and easily. Another aim of the Initiative is to develop new cancer therapies. Better systems for data synthesis would inform drug development with richer and more accurate insights from the 'omics' sciences, animal studies and early human trials. Moreover, health-care funders such as Britain's National Health Service and Medicare in the United States could better understand a drug's benefits and harms in the real world by synthesizing data from clinical trials, cohort studies, patient experiences reported through mobile and social applications, and drug-surveillance systems. We are not proposing a one-model-fits-all approach," the authors conclude, "but society does not need more islands of data analysis that support conflicting inferences. As large and diverse data sets become ever more plentiful, we must ensure that rigorous and trustworthy methods to make sense of the data are developed in parallel."

This is also what the AIFA proposes to achieve by implementing and making good use of its own databases.

5. Dementia and Alzheimer's. Future "epidemics" and treatment prospectives

All the most credible international estimates agree on the fact that there will be more than 135 million patients suffering from dementia in 2050, with enormous social and economic costs as a consequence. Dementia, of which Alzheimer's Disease is the most common form, is causing a real international emergency and, together with mental illness, is one of the epidemics that, in the future, will have a major impact on healthcare systems. The factors at the root of these diseases are still unclear, what is certain is that they are caused by the degeneration of cerebral neurons due to various physiopathological mechanisms. Research in the field of neuroscience has confirmed that the pathological processes that lead to neuronal death over the years start 15-20 years before the appearance of clinical symptoms and therefore the possibility opens up, though as yet not confirmed, of diagnosing the disease in its initial stages through the use of biomarkers. This would allow early treatment and possibly the slowing down of the neurodegenerative process that leads to the loss of higher cognitive functions. From the regulatory point of view, a collective effort is required to rapidly accumulate and share epidemiological, clinical and neurobiological data that enable the verification of the biomarkers, the new diagnostic criteria and the resulting measures. The Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA), together with other very important public and private partners, takes part in initiatives aimed at drawing up new development models and clinical trials that enable confirmation of the potential of the new treatments in modifying the neurodegenerative process, currently considered unstoppable.

5.1 Dementia: the new global epidemic

The estimates of the World Health Organisation of the number of patients currently suffering from various forms of dementia around the world and the economic and social burdens that these diseases bring are truly alarming. We are talking about 47 and a half million individuals in 2015 alone, a figure that is destined to almost double within only 15 years. The global cost for dementia in 2010 amounted to more than 600 billion dollars, 1% of the Gross National Product of the entire world. Shocking data, and alas accurate, that require the collective action of governments, science and civil society to find pathways to treatment as soon as possible.
The International Medicines Agency is taking a prominent role, together with other new international medicines agencies and the British government, in a multilateral forum established for the purpose of reconciling research and regulatory science in an integrated approach to identifying possible treatment pathways for dementia. It was not by chance that, on the 9th and 10th of June, 2015[64] the Agency hosted one of the meetings at the heart of the "Dementia Integrated Development" programme, during which academics and regulators met in order to advance the actions undertaken following the challenge launched by the first G8 summit on Dementia two years ago to find a treatment to modify the disease by 2025.
The work of the Dementia Integrated Development programme is led by Raj Long, Senior Regulatory Officer of the Bill & Melinda Gates Foundation and a member of the World Dementia Council, who, July 21st of last year, at the international conference of the Alzheimer Association in Washington, presented an independent report[65] on what has been achieved so far and future actions.
The document summarises the work carried out and proposes recommendations and concrete actions that can be implemented by research and regulatory science to try to overcome the current impasse in the development of new treatments. In relating his own process of understanding, first of all, what and where the main obstacles are that are delaying the discovery of innovative medicines for dementia, Long reiterated the methodology by which he managed to identify a series of possible actions, the outcome of the analysis of past and present scenarios of clinical research in the field, listening to the needs of patients and, above all, the regulatory point of view. The medicines agencies, indeed, are playing a fundamental role since they can operate by acting not only on the authorisation procedures, favouring adaptive or conditional pathways, for example, to enable access to future treatments, but also scientific advice at all the stages of clinical development. The close international collaboration between agencies is therefore a factor in optimising efforts and there are many attempts at comparison for the pur-

[64] http://www.agenziafarmaco.gov.it/it/content/emergenza-demenze-le-agenzie-regolatorie-di-tutto-il-mondo-si-incontrano-aifa-affrontare-il-.
[65] https://www.gov.uk/government/publications/challenges-to-finding-treatments-for-dementia.

pose of making uniform, as far as possible given the legislative differences, the development plans at the global level, avoiding duplication.

In dementia, as in no other therapeutic area, the highest rate of failure of trials has unfortunately been recorded, especially in the early phases. As a consequence, it is destined to become a field of little commercial interest, given the huge investments required that have so far produced little or no return. More than ever, this has become a real emergency, as already demonstrated.

This is compounded by a number of gaps in knowledge about the causes and physiopathology of the disease that may, in part, explain the series of failures in scientific progress in this area. In this regard, it would be desirable to be able to draw upon experience from dealing with diseases of similar complexity, such as HIV, oncology and rheumatoid arthritis. For this reason as well, the contribution of those regulators who, in the course of their professional careers, have participated in scientific conquests in these therapeutic areas is of fundamental assistance.

The 10 medicines agencies involved in this ambitious project are concentrating on 6 different fields of intervention, each one led by an individual country. The AIFA, in the person of Valentina Mantua, psychiatrist and medical director at the European Assessment Office, is leading the working group examining the application of modelling and extrapolation. The population of patients with dementia, especially in the early stage, so far enrolled in clinical trials are, in fact, very heterogeneous, probably also with differences at the biological level. This heterogeneity is, in part, responsible for the difficulty in evaluating the response to treatments. The challenge accepted by the working group is to study homogenous subpopulations that are highly distinct from a biological point of view (for example, families with autosomal dominant mutations) and to extrapolate the disease model to infinitely more complex sporadic forms in order to define the patients in a more precise way.

Never before in the field of dementia research have 10 responsible authorities come together to form a coalition. It is a powerful concentration of strategic drivers that can truly shape the

progress of regulatory science. Their potential, Raj Long underlines, must be legitimised by the collective support of individual governments and researchers working together. The successful outcome of this collaboration will be an enormous incentive for regenerating investment in the development of medicines for dementia and for overcoming the current impasse.
As Long concludes, for the 47.5 million patients suffering from dementia around the world, "doing nothing" is not an option. Nor is *"doing the same thing over and over again and expecting different results, because that would be madness"* (commonly attributed to Albert Einstein).

5.2 Immunotherapies for Alzheimer's: state of the art and outlook

Alzheimer's Disease (AD) is the most common form of dementia (60-70% of cases) and is one of the major public health problems, impacting significantly on the global costs of non-communicable diseases. Currently, around 8 million new cases are recorded every year and epidemiological studies suggest that we are only at the dawn of a global epidemic of this disease. The number of people suffering from various forms of dementia seems destined to double every 20 years, reaching 75.6 million cases worldwide in 2030 and 135.5 million in 2050. Even if these estimates are double the actual amount, that would still represent a very high prevalence.

Notwithstanding the efforts poured into research, the current treatments provide only marginal symptomatic benefits and are not effective in preventing or modifying the disease. The progression of the disease is not well known but it is thought that, at least in part and for certain forms of AD, it may be connected to the altered metabolism of the proteins β-amyloid and tau, which manifests as an accumulation of β-amyloid plaques and tau neurofibrillary tangles (NFTs) in the brain.

Nor are the causes of AD yet known. Around 1% of the early-onset familial forms have autosomal dominant heredity due to mutations of three main genes, APP (Amyloid Precursor Protein), Presenilin 1 and 2 (PSEN1 and PSEN2). Most cases of late-onset AD, on the other hand, have a multifactor pathogenesis with a significant genetic component that contributes, together with metabolic factors, such as insulin-resistance, and environmental ones, such as diet and physical exercise, to the phenotypical manifestations of the disease. The study of the early-onset forms, although rare, has shaped current understanding of the physiopathology and natural history of AD, as well as the development of therapeutic targets and the design of clinical trials. It is yet to be established, however, how much data from the study of autosomal dominant forms can be extrapolated to the sporadic forms.

One of the therapeutic approaches currently being evaluated consists of removing fragments of amyloid beta peptide (Aβ) from the brain by means of anti-Aβ antibodies. Aβ immunotherapy is uncovering a potentially promising treatment strategy based on human neuropathology and pre-clinical studies. In active vaccination against Aβ42, the patients receive injections of the same antigen, in passive vaccination of patients, monoclonal antibodies (mAb) are used against various portions of β-amyloid peptide (soluble, deposited, oligomeric).

Active immunisation and passive immunisation against the beta-amyloid protein in transgenic mice specimens caused an increase in the clearance of deposits of amyloid plaque and the improvement of cognitive performance, while brain imaging and neuropathological studies suggest that active and passive anti-Aβ immunotherapy could, perhaps, reduce the quantity of β–amyloids deposited in plaques or soluble in the brains of those suffering from Alzheimer's[66].

[66] http://www.ncbi.nlm.nih.gov/pubmed/25483498.

AN1792 was the first active immunotherapy product for AD that used a fragment of amino acid (Aβ42) as an immunogen; nevertheless, a phase 2 trial of the anti-amyloid was halted due to the appearance of meningoencephalitis in a small subgroup of patients. Notwithstanding this hold up, the long term follow-up of patients immunised with AN1792 displayed a reduction of the functional decline in patients who responded to the antibody, supporting the theory that Aβ immunotherapy could have functional benefits in the long term. In this regard, new immunogens with shorter peptide sequences that can avoid autoimmune response to Aβ42 are in development.

Among the passive immunotherapies, the results of two large-scale phase 3 clinical trials in patients with mild to moderate AD using bapineuzumab, a humanised monoclonal antibody targeted at the N-terminal sequence of Aβ, were disappointing: the desired therapeutic effect was not attained[67].

Even solanezumab (a monocolonal antibody developed against the soluble monomeric forms of Aβ and directed at the average region of Aβ), did not attain the primary endpoints in two phase 3 trials in patients with mild to moderate AD. Another phase 3 trial with solanezumab in patients with mild AD is currently underway, based on the encouraging results encountered in the statistical analysis of this subgroup[68].

Other more recent approaches, such as the systemic co-administration of clioquinol and Aβ42 vaccines, significantly reduce Aβ deposits in the brain of transgenic mice with AD. In non-rodent specimens, the rapid improvement of the cognitive dysfunction in dogs with amyloid immunotherapy would suggest the importance of the use of canine specimens to test vaccines for AD.

The so-called "arctic mutation" leads to the formation of soluble protofibrils of Aβ, a type of Aβ that was found to be neurotoxic (more than insoluble fibrils) and that appears to be present in all cases of AD. A monoclonal antibody, mAb158, was developed to reach the Aβ protofibrils with a high degree of selectivity (at least a thousand times higher for protofibrils compared to Aβ monomers). A humanised version of the mAb158 antibody, BAN2401, is currently in a phase 2B clinical trial, so far without the serious safety problems that arose in the previous phase 1 and 2bis clinical trials. Experience in the field indicates the importance of starting treatment early in the course of the disease and increasing the number of studies to improve the accuracy of diagnosis. Indeed, with the study underway, amyloid PET is used to enrich the population of patients at an early stage[69]. BAN2401 is a promising candidate for Aβ immunotherapy in the early stage of AD. Other encouraging efforts in immunotherapy, as well

[67] http://www.ncbi.nlm.nih.gov/pubmed/24490853.

[68] http://www.ncbi.nlm.nih.gov/pubmed/24981190.

[69] As suggested by us in the work "Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: Cerebro- spinal-fluid related biomarkers for drugs affecting amyloid burden – Regulatory considerations by European Medicines Agency focusing in improving benefit/risk in regulatory trials", *European Neuropsychopharmacology* [2011] 21, 781-788.

as in the field of small molecules, offer cautious hope that truly innovative treatments for AD may be found in the future[70].

The second generation of active Aβ vaccines (CAD106, ACC-001 and Affitope AD02) and the new passive anti-Aβ immunotherapies (gantenerumab and crenezumab) have been developed and are in the clinical trial phase (CAD106, ACC-001, e Affitope AD02 are in phase 2). Gantenerumab and crenezumab are being tested in clinical trials that are enrolling patients with mild AD and so-called prodromic subjects with initial cognitive alterations. Moreover, gantenerumab and solanezumab are also being studied in pre-clinical patients with autosomal dominant mutations from AD, but without cognitive symptoms.

Until now, the major limitations of Aβ immunisation included the development of encephalitis, the lack of clinical improvement and the absence of any effect on the neurofibrillary tangles (NFTs), which are another important neuropathological characteristic of AD. Other critical points concern the design of the trials and various essential variables for optimising trial designs and improving the conditions of the participants.

Due to the central role of NFTs in dementia, immunotherapy that targets these Tau protein aggregates is an important area of the research. In particular, active immunotherapy that targets the epitope phospho-Ser422 has proved effective, with the consequent clearance of the Tau protein and improvement of the cognitive deficit caused by the disease correlated with the Tau protein in a well-defined transgenic specimen. As with the Aβ oligomers, the assumed role of the oligomers of the Tau filaments in the physiopathology of AD has led to them being investigated as potential targets of immunotherapy for AD and for diseases correlated with the Tau protein. Overall, these results suggest that immunotherapies that only target Aβ may not be sufficient to modify the disease. To this end, researchers have begun to check whether intravenous immunoglobulin (IVIG) can be used as an alternative immunotherapy strategy[71].

IVIG is a mixture of natural human antibodies (immunoglobulin G) derived from the plasma of health young volunteers. IVIG was used for almost half a century for primary humoral immune deficiencies and autoimmune syndromes in particular and, more recently, for a series of neurological disorders, such as chronic inflammatory demyelinating polyradiculoneuropathy and Guillain-Barré syndrome. The rationale for the use of IVIG in the treatment of AD is based on a series of reasons. It has been seen that IVIG presents high levels of antibodies against different conformations of monomers and Aβ aggregates, but its repertoire of natural antibodies could also be used to normalise the inflammatory component of AD. IVIG's security profile for other diseases has also mitigated concerns over clinical trials on AD.

[70] http://www.alzres.com/content/6/2/16.

[71] http://www.eurekaselect.com/123950/article#.

Nevertheless, notwithstanding the initial promise of the phase 1 and 2 clinical trials conducted in Germany and the United States, a recent multicentre, phase 3, double blind trial on 390 people, called Gammaglobulin Alzheimer's Partnership (GAP), did not attain the primary endpoints of slowing down cognitive and functional decline. The results of the GAP study could support IVIG's positive safety profile and have demonstrated potentially beneficial effects for pre-specified subgroups with moderate AD and with apoE4 vector. In conjunction with these clinical trials, various pre-clinical experiments have shown that IVIG is a neuroprotective against Aβ toxicity *in vitro* and improves the Aβ clearance *ex vivo*, mediated by microglia, while the *in vivo* administration of IVIG reduces inflammation in AD transgenic mice. The action mechanism of IVIG is still of great interest and it remains to be confirmed to what extent optimised doses of IVIG, provided sufficiently early in the trajectory of the disease, could prove useful in modifying the progression of the disease, while we still can.

6. Beyond the limits of science?

The history of mankind is the story of the will to overcome, to improve, to experiment. A desire that results in taking substances or using external devices that enhance human features and faculties. The use of pharmacological treatments by healthy individuals to increase their cognitive performance or neural implants to stimulate certain areas of the brain are two sides of the same coin. Neuro-Enhancement (NE) is a recognised global reality, the extent of which is still unknown and the implications of which give rise to various problems, especially of an ethical and regulatory nature, as yet unresolved.

6.1 Reality and science fiction: progress in the field of neural implants

Memory chips that enable everything ever read to be remembered perfectly, Internet interfaces implanted in the brain that convert thoughts into online searches, wafers on solid retinal layers that enable the wearer to see perfectly in the dark, cochlear implants that enable any conversation in a noise environment to be heard and so on. These are not fantasies from the pen of Philip K. Dick, a visionary author who has written numerous science fiction novels from which movies have drawn their plots, but it is a reality that may not be far away: the alliance between man and machine is being forged.

Unlike pacemakers, dental crowns or insulin pump implants, neural prostheses, devices able to restore or complete mental capacity through electronic systems inserted directly in the nervous system, change the way in which the world is perceived and moved through: for good or ill, these devices are becoming part of us.

In reality, neural prostheses are not really new. "Bionic ear" cochlear implants transmit sensorial information to the nervous system and are indeed neuro-prostheses; on the market for more than three decades, they have been used by 300,000 deaf patients worldwide. Conceptually similar, the implants of retinal prostheses carried out by a group of researchers from a Californian company enable a degree of visual function to be regained. The result of an important study that demonstrates their effectiveness was published by the review *Frontiers in Neuroprosthetics* in 2012 and, after authorisation of the device in the United States and Europe, several dozen patients regained a degree of visual function as a result. The device is made up of miniscule electrodes connected to the retina that can intercept visual information through a micro camera mounted on a pair of special spectacles; the images recorded are sent to a receiver that, through a processor, decodes the video signal. This information is sent to an antenna able to communicate with the electrodes that, in turn, transmits signals that can stimulate the optical nerves, responsible for the "passage" of images from the eyes to the brain.

Another type of implant now common, used by thousands of patients suffering from Parkinson's disease worldwide, is a neurostimulator that sends electrical impulses deep into the brain, activating certain mechanisms involved in motor control. Electrodes or electrocatheters are placed inside the cerebral tissue and connected by a wire that runs to a battery under the skin; recently, a new surgical technique has been developed to implant electrodes that exploits advances in diagnostic imagining, illustrated in an article in the *Journal of Neurosurgery*. The effect of the implant is to reduce or eliminate tremors and rigid movements due to Parkinson's disease (even though, unfortunately, the device does not halt the progression of the disease). Experimental trials are underway to test the effectiveness of this "deep brain stimulation" in the treatment of other disorders.

Electrical stimulation can also improve certain types of memory, as demonstrated by the neurosurgeon Itzhak Fried and his colleagues at the University of California, Los Angeles, in an article published in 2012 in the *New England Journal of Medicine*. According to Fried, the secret of "external" memorisation is to stimulate the hippocampus, a region of the brain assigned to the construction of long-term memory. Using a similar configuration to a video game in which patients identify with a taxi driver obliged to remember the intricate roads of the city and deal with customers getting in and out, researchers obtained an unexpected result: patients managed to orient themselves much better, recognised points of reference and turned in the various streets with greater agility.

Not all brain implants function by directly stimulating the brain. Some work by reading the signals from the brain in order to interpret, for example, the intentions of a paralysed user. Optimal systems of neural prosthesis should try to do both these things. How long will it be before devices like this are available? To start with, scientists, doctors and engineers must find a safer and more reliable way of inserting probes into people's brains. For now, the only option is to make small holes in the cranium and insert long, thin electrodes until they reach their destination inside the brain: however, this carries risks of infection.

External devices like caps or headset that enable simple operations to be carried out by exploiting the intensity of brain waves, are being used to control mobile phones and video game characters with applications also in the medical field and do not display these risks, but they are also much less effective. Brain-machine interfaces must be inserted directly into the brain in order to be able to collect the signals from the nerve cells, but there are difficulties connected to the relatively short duration of these devices. Part of the problem is mechanical: an implant that moves even a millimetre can become ineffective. Another aspect of the problem is biological: the implant must be non-toxic and biocompatible in order not to provoke an immune reaction. It must also be quite small in order

to be completely enclosed within the cranium and it must have low energy consumption. Many researchers are trying to overcome these problems; among them are the electronic engineers Michel Maharbiz and José Carmena and their colleagues at the University of California, Berkeley, who are developing a wireless brain interface, a sort of "neural powder": thousands of biologically neutral microsensors, measuring around a tenth of a millimetre, convert electrical signals into ultrasound that can be read outside the brain. Once again, reality and fiction are coming together: indeed, the two engineers were asked to collaborate in the latest film by Wally Pfister, "Transendence", a science fiction thriller about artificial intelligence. But this is not just about leisure and entertainment: as Michel Maharbiz says: "Once implants can be made 'lifetime stable' for healthy adults, many severe disabilities... will likely be chronically treatable." For millions of patients, neural implants will literally change their lives.

Assuming that we will be able to overcome the barriers of bioengineering, the next challenge will be interpreting the complex information originating from around 86 billion miniscule nerve cells that make up the brain. We are already able to do it, but in a limited way.

On the basis of decades of research into non-human primates, John P. Donoghue, Leigh R. Hochberg and their colleagues at Brown University have created a system that can decode neural signals and enable robotic devices to be controlled by thought. A small chip, dotted with around 100 needle-shaped wires, is inserted into the part of the neocortex that controls movement; the motor signals are fed to a computer that decodes them and distributes them to external robotic devices. In a study published by researchers at Brown University in *Nature*, the results were given of two patients long paralysed due to strokes, a woman aged 58 and a man 66 years old; the woman, in particular, was able to pick up and sip a soft drink without assistance for the first time in 15 years. The safety and feasibility of this brain-computer interface, called *BrainGate* and destined to bring robotics and innovative technologies under the direct control of the human mind, is now being evaluated.

For now, guiding a robotic arm in this way is uncomfortable and difficult: we are far from neural implants with the precision and reactivity of a computer keyboard. More precise instruments are required that lead to a more detailed understanding of the various types of nerve cells and how these fit together in more complex circuits. For example, the images obtained from functional magnetic resonance do not have sufficient resolution to give us real mastery of the neural code; every voxel in an ultrasound scan of the brain contains half a million to a million neurons, but it would need to be calibrated on a single neuron.

One of the most promising instruments in field is optogenetics, which draws on a combination of optics and molecular biology: this technique uses light to activate or inhibit neurons that, being genetically engineered, manage to respond in a precise and effective way to light.

Advances in molecular biology, neuroscience and electronics will almost certainly lead, in

time, to smaller, more intelligent, more compact and more efficient implants. A time will come when neural implants will not only be used for serious problems like paralysis, blindness or amnesia but also for people with less traumatic disabilities. They may be used to enhance the performance of healthy people, to improve the memory, mental concentration, even the mood.

A programme underway at the Pentagon's *Defense Advanced Research Projects Agency* (DARPA) into the development of new technologies for military use is already supporting work on brain implants that improve the memory to help soldiers wounded in war, and from here to "supersoldiers" is a short step. Will we perhaps end up with the "amplified" humans imagined by the author Daniel Wilson, people with mental capacity amplified by technologies who excel in daily life, in science, sport and armed conflicts? These questions challenge society in new ways and open up possibilities that we can scarcely imagine.

As William Gibson, science fiction writer and an exponent of cyberpunk, said "The future is already here, it's just that it is badly distributed."

6.2 The enhancement of cerebral performance and the Ethical and Regulatory problems

The history of mankind can also be told through the drive to overcome limitations, to always go beyond the boundary between what is and what could be. Many of the gains that have forever changed our way of experiencing and interpreting the world - the capacity to make tools, the invention of printing, the Internet, biotechnologies - respond in some way to this need to exceed the limits. In recent years, however, the desire to improve the human condition has taken different forms that require deeper reflection on the ethical and scientific-regulatory aspects. Unlike in the recent past, the search for ways of bending the environment to the will and needs of mankind, that is to say, what is commonly regarded as "progress", is no longer evident but, instead, there is an attempt to adapt the new-man to the "man-environment" (man on man) by acting directly on the brain in order to attain the universal desire for real improvement, once and for all, of all cognitive performances. This means acting on the physical body and the psyche to make the ancient dream come true of superior performance, the aspiration to be more skilful, more efficient, to extend life and remain "intelligent" until the end of life.

These issues have long been discussed in all the cultural, political and scientific arenas where human actions are reflected. How could we forget the cult film "Blade Runner" depicting Nexus-6, mutants programmed to have superior performance; or the search for artificial intelligence or the eagerly awaited applications of nano-technologies. A worldwide debate is currently underway on enhancing the brain, also known as Neuro-Enhancement (NE), because the implications arising from this lead to problems as yet unresolved. On one hand, in fact, pharmacological treatments are available that are able to improve the symptoms of existing diseases, such as Attention Deficit and Hyperactivity Disorder (ADHD), which, by increasing attention levels, impact on the cognitive activity in a positive way; on the other, there is the use by healthy people of treatments such as psychostimulants and antidepressants, for example, to increase professional, sports and even social performance. In the first case, the use of medicines to treat hyperactivity when the diagnosis is certain and the treatment properly carried out changes the lives of many children, allowing them to attain goals that otherwise would have been impossible: a degree, a driving licence, a normal social, family and working life. Early treatment is of particular importance in the results that can be obtained and also that it is administered during the neurodevelopmental period. If access to treatment comes too late, many developmental stages, such as, for example, the academic levels that can be achieved, are precluded, compromising the ability of the child or adolescent to determine their own future in accordance with their aptitude.

In the second case, NE is used by healthy people who decide to expose themselves to risks

of side effects and dependence, departing from the classic concept of treatment. This opens up problems of an ethical, scientific and regulatory nature. For now, the effectiveness in healthy people has only been demonstrated under extremely controlled experimental conditions. It is therefore a matter of evaluating, based on the current state of knowledge, the real risk/benefit ratio and the true added value. There are problems to be tackled across a broad spectrum that includes the harmonisation of the definition of NE, as yet without consensus, the population to be studied, the measurement of the efficacy and duration of the therapeutic action. An agreement must be found on the endpoints and the impact on the quality of life, and knowledge must be acquired about what happens when, for example, taking these substances must be halted for any reason. Finally, the safety of their long-term use must be evaluated; moreover, there are profound differences between the various countries on the level of chemical manipulation permitted and the possibility of self-experimentation in a more or less extreme way. These are issues to be tackled at a global level, for which data and knowledge must be shared since this is confidential research, at least in principle, on a small number of patients and only the ability to create worldwide networks will enable significant results to be obtained for subsequent analysis.

This is one of those examples where Science with a capital S must be repositioned in the regulatory decision-making processes, perhaps assigning resources to experimental research and optimising our ability to quickly incorporate the results of pre-clinical research in clinical practice. We are permeated by a humanistic culture that has brought our country world renown but, in recent years, we have been faced with a cultural drift that tends to exclude technical knowledge from the decision-making processes, with a worrying loss of scientific literacy that, paradoxically, guides public opinion towards conservative regression, dominated by an understandable emotional instability faced with natural processes like disease, the choice of lifestyles or the attitude to medicines and treatments. Neuro-Enhancement must take account of the extraordinary capacity of the human brain to image things that are not yet real; the frontal cortex can, in fact, simulate non-existent situations, thereby driving mankind's natural compulsion to go beyond its limits. But it is important to take care not to exceed those limitations imposed by human physiology, such as the need for sleep and food, because when the fundamental hardware of biology is tampered with, one must be ready to accept the consequences. We are, of course, talking about the human brain and it is on this organ, the most delicate and sophisticated in our bodies, that, in the final analysis, NE acts. No subjects that have undergone eternal enhancement can be found in history or clinical evidence, perhaps because, to quote the celebrated phrase from "Blade Runner": "The light that burns twice as bright burns for half as long." There are ethical considerations to be tackled, beginning with the level of self-determination that must be guaranteed with regard to the level of assistance to be delivered and any costs for the National Health Service.

There is a problem regarding the level of knowledge required to make an informed decision to submit to these treatments even in the absence of disease. Finally, checks must be carried out to uncover any acts of manipulation for commercial purposes. Any access to NEs, whenever they reach the stage of regulatory assessment, must therefore be linked to dedicated Monitoring Registers for the purpose of detecting the greatest number of the most homogenous data possible. This is a recurring problem in psychopharmacology since there is great variability in the phenomenological expression of the same disease and symptomatological manifestations that are common to different diagnoses.

Another aspect, no less important, concerns the evaluation of treatments for which certain safety and efficacy data in healthy volunteers over very long periods of time, potentially decades, which could mean the period of their use in real life, will not be available in the short term. Perhaps it is still too soon to say, but should they come, these treatments will be a scientific and regulatory challenge never before faced.

7. The defence of regulatory science

The course followed by medicine and pharmacology from their beginnings to the present day is the story of impetuous but certainly not linear development. A story that began at the dawn of mankind that was nurtured by the latter's curiosity about the elements (plants, fruit, extracts and potions) that could cause an alteration of the human condition. It is well known that the word phármakon *was used in ancient Greece to mean both "medicine" and "poison", bearing witness to the first uncertain steps of medical science in the West. Many centuries later, the picture appears remarkably transformed: a little more than 70 years since the first use of penicillin, the pharmaceutical world is assimilating the contribution of genetics and genomics, quantum physics and Big Data. From small molecules, we have developed biotechnological medicines that can act on personalised targets, while further revolutions are on the horizon that will redraw the boundaries still more of what we call "treatment." Notwithstanding all this, the "magical-priestly" component of primordial medicine has in no way been eradicated. News regularly breaks in the worldwide media about treatments, protocols and "miraculous" remedies. A closer look reveals some features they have in common. The anecdotal nature of the observations, the presence of charismatic figures, the championing of an alleged esoteric truth, shared only with the circle of initiated, over and above knowledge validated by "official science". The rejection of the scientific method and institutions is a common thread that runs through our society and connects many movements with different causes and objectives. From the attempt to deregulate advanced treatments to the rejection of vaccination, the health intervention of greatest success in history, according to the World Health Organisation, and the weapon that enabled us to wipe out diseases considered fatal until the last century, the examples are plentiful. One of the tasks of a regulatory agency like the Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA) is the defence of science and its founding principles and recent years have been replete with battles in which the Agency's voice has been raised against those who have tried to discredit and delegitimise the health institutions and who operated against the Italian and international regulations. One of the most sensational affairs, both for the seriousness of the events and the enormity of the media response it evoked, was the "Stamina case." After a muted start and a few mentions in the local news, it rapidly turned into a legal-media-institutional uproar of gigantic proportions that took on dramatic implications and gave rise to debate that could be described euphemistically as "very lively". Many texts are included in this publication that the AIFA has produced, acting at the forefront through its institutional representatives or amplifying the voices of the greatest Italian and international scientists who have railed many times against the serious violations of "predatory pseudoscience". In the clear and unequivocal words of the first decree in the history of the AIFA, the one issued in May 2012 prohibiting the "sampling, transport, manipulation, cultivation, storage and administration of human cells at Brescia City Hospitals in collaboration with the non-profit organisation, the Stamina Foundation" (which, it was also discovered later, was not even a non-profit*

organisation!) and those of the reconstruction in the judicial conclusion, an entire nation was revealed. A snapshot of Italy emerged that revealed its fragilities and strong points, its undeniable tendency to dance on the edge of the abyss and its capacity to deploy the force and energy of its best citizens to avoid falling in. From the editorials published, cyclical questions emerge, ghosts that pursue us and remind us of the darkest pages of our history from the point of view of respect for scientific rules. Important hints and warnings can be drawn from the events of recent decades and should be kept within reach for the time when, in the near future, new attempts to champion fake treatments and exploit suffering could reappear, fatally, on the horizon. As the exponent of critical realism George Santayana wrote: "Those who do not remember the past are condemned to repeat it." If we add to memory the detailed analysis of what has happened, a potent immunisation is available against the virus of pseudoscience.

7.1.a Scientific progress cannot be stopped by emotions

No model yet exists that is able to replace experiments on animals but this type of test is only used after having established in the laboratory that the molecule has potentially therapeutic effects.
After the threats received by Caterina Simonsen, a young woman of 25 years of age suffering from 4 rare diseases who said she was alive thanks to experiments on animals, and, thereafter, the recent demands to include phrases concerning tests carried out on animals and humans on the packaging of certain medicines, I believe it to be my duty to restate the importance of studies on animals and to make clear that medicines are not products of ordinary consumption and, therefore, it is not possible to display various warnings on their packaging that have not been unequivocally agreed at the international level. Very precise rules must be respected, according to which no regulatory agency in the world can independently decide what to write on the packaging of a medicinal product. Specifically, in our country we are obliged to comply with a Community Code concerning medicines for human use (which was enshrined in law by Legislative Decree no. 219 of 2006) that lays down that every medicine must complete all the study phases for non-clinical and clinical trials before the AIFA can issue a Marketing Authorisation.
No medicine can, in fact, be marketed in Italy without the authorisation of the AIFA, the regulatory authority designated to protect public health, ensuring the quality, safety and efficacy of all the medicines on the market. Once the Marketing Authorisation has been granted, this becomes the medicine's passport, since it establishes its name, its composition, a description of the method of manufacture, the therapeutic indications, contraindications and adverse reactions, the posology, the pharmaceutical form, the method and pathway of administration, the precautionary and safety measures to be adopted for storage and administration to patients, a model of the external packaging, the assessment of the risks the medicine may pose to the environment and, above all, Summary of Product Characteristics and the Illustrative Leaflet. The latter are the only official documents that enable the main characteristics of authorised medicines in Italy to be known and have also been available online since November 13, 2013 in the Medicines Data Bank of the AIFA, the first data bank to be certified and updated in real time.
In this case, both the Summary of Product Characteristics and the Illustrative Leaflet (which gives information in simpler language for members of the general public) must be compiled in accordance with unequivocal rules, pursuant to attachment 2 of the Community Code. The Summary of Product Characteristics is, in fact, laid out according to an established model, identical through Europe and also used in similar forms in countries outside the European Union. It contains a section specifically dedicated to pre-clinical safety data obtained from laboratory animals. In the field of medicines for human uses, experiments on animals are

fundamental in all the countries of the world, since the alternative methods available are not yet sufficient to completely replace tests carried out on animals that have organs, apparatus and chemical mediators in common with humans. Current international and national regulations that govern the development and marketing of pharmaceutical products therefore make it mandatory to carry out these tests before undertaking clinical trials on humans. In other words, in developing a medicine, a pre-clinical trial phase must be carried out, based, that is, on the effects and above all the toxicity of a potential medicine on animals.

Currently, abolishing animal experiments would mean halting medical progress and impeding the development of medicines that could save the lives of millions of people (including numerous children).

To observe how a new molecule behaves and its level of toxicity (how it is absorbed and subsequently eliminated in a complex living organism), to understand, for example, whether a medicine acts on pain, vomiting or the memory, cells cultivated *in vitro* are not enough, far less the bioinformatic and computational models. The study of dedicated animal models is fundamental. Strict safety tests that involve certain animal species, always under controlled conditions and only when absolutely necessary, enable the safety of a medicine to be assessed before being made available to humans and are therefore indispensable to avoid real tragedies. Let us not forget the disaster caused by Thalidomide, a hypnotic sedative medicine, that was introduced in 46 different countries between 1958 and 1960 in accordance with the regulations then current, without a specific non-clinical trial into reproductive toxicity and teratogenicity, which caused the birth of 10,000 children worldwide with severe malformations, forcing the governments of various countries to tackle the question of the inadequacy of clinical trials and the need for greater controls before putting new medicines on sale on a global level. A disaster that would have been possible to foresee and avoid if only more tests had been carried out on animals. This need to provide regulatory agencies, rules, regulations and guidelines for the assessment of data on the safety, quality and efficacy of medicines and the consequent common effort aimed at standardising the rules on the conduct of the trials required to support the development of a medicine, led in 1990 to the creation in Paris of the International Conference for the harmonisation of the technical prerequisites for registering medicines for human use.

The current process of approving a medicine is therefore the outcome of scientific knowledge acquired in the last 60 years and constitutes an as yet irreplaceable tool for experimenting on and registering quality medicines that are reasonably safe and effective for patients. This is a process that requires the application of an internationally codified methodology, abiding by legally binding rules in compliance with regulatory guidelines and in accordance with the rules of good manufacturing, laboratory and clinical practice. The release of a medicine on the market is necessarily preceded by the possibility of synthesis on a sufficient scale and the development of suitable pharmaceutical forms, pharmaco-toxicological *in vitro* and *in vivo* experiments (non-

clinical trials) and then strictly controlled clinical research (phase 1 on healthy volunteers, phases 2 and 3 on the sick). Non-clinical experimentation involves pharmacodynamic studies *in vitro* and non–human animal trials, fundamental to determining the main therapeutic characteristics, side effects and the duration of a medicine's action. This phase includes pharmacological, toxicological, toxicokinetic and pharmacological safety studies, with the potential extension to pharmacokinetic and bioavailability studies. Most of the animals are used in safety and toxicology studies, conducted at sites controlled by the inspectors of the Ministry of Health and the Higher Health Institute. Initially, *in vitro* studies are carried out in order to understand the characteristics of the chemical molecule from which it is thought a medicine can be obtained (the substance is put in a test tube together with cell culture or microorganisms and subject to a series of highly specialized laboratory tests) and, only after it has been established in the laboratory that the molecule possesses potential therapeutic effects, does the process continue with experiments on animals (*in vivo* studies). Currently, this is a fundamental step in the development of a medicine and the cornerstone of studies that precede trials on humans.
We hope that, in the not too distant future, thanks to progress in medical science, the current research model can be superseded. That time has, unfortunately, not yet arrived and the scientific data tell us that animals remain an irreplaceable model in understanding the characteristics of many diseases and in the development of medicines able to combat them. We cannot fail – allowing once again often false and uncontrolled emotional responses to prevail – to recognise that scientific research is one of the utmost expressions of human ingenuity and contributes to the quality of life, the level of wellbeing and the competitiveness of a country and all its citizens.

7.1.b "Miracle cures": the voice of patients in the Guide "I don't have anything to lose by trying it"

In response to numerous requests for clarification on how to use the Guide, which warns against miracle cures, the AIFA makes clear that the document can be freely downloaded and printed (it is laid out for printing on normal paper and by digital printers), it is free of copyright but cannot be amended in any way. *Sense about Science* produced this guide by working with patients, health operators, doctors, nurses and charitable institutions, examining the methods used to analyse, in the light of the evidence, sensational claims and then take decisions about one's own health.
The Guide was produced with the collaboration of associations of English patients suffering from various diseases, from multiple sclerosis to cancer, from Alzheimer's to epilepsy, from liver diseases to neurological disorders: Alzheimer's Society, Asthma UK, Breakthrough Breast Cancer, British Lung Foundation, British Thyroid Foundation, Cancer Research UK, Core Charity,

Epilepsy Research UK, Europe PMC, HealthWatch, INVOLVE, Motor Neurone Disease Association, MS Society, Muscular Dystrophy Campaign, NIHR Diabetes Research Network, Parkinson's UK, UK Cochrane Centre, World Cancer Research Fund and Science Communicated.
"It is very important that the safety and efficacy of treatments are based on the evidence, otherwise we will be chasing rainbows every day." These are the words of Jane Tomlin, a women suffering from multiple sclerosis, who decided to publicly share her struggle with this serious condition, in the attempt to act as a warning against "miracle cures" championed by unscrupulous, incompetent individuals.
This, and the accounts of other patients, are contained in "*Non ho nulla da perdere a provarlo*", the official Italian version, produced by the AIFA, of the Guide "I've Got Nothing To Lose By Trying It."
The philosophy behind "I've Got Nothing To Lose By Trying It" is that of a handbook for patients, written by patients. Publications make available to readers a wealth of knowledge, often gained through disappointment and painful experiences, which may prove vital in avoiding the sick making errors when taking delicate decisions concerning their health.
The proclamation of a wonder drug or an alleged cure, in fact, gets more headlines than the statements of thousands of patients who have discovered for themselves the failure of treatments without scientific foundation and the ensuing disappointment, with sometimes devastating effects. The emotional burden, as well as the financial cost and the time lost on ineffective and often potentially damaging treatments, is more often than not underestimated. But the psychological component in tackling the disease can make the difference between good or ill. For this reason, giving voice to patients who have encountered failure and who, unfortunately, are not always heard, can be useful to those who feel disoriented and do not know in whom to trust.
With the publication of this handy manual, full of useful suggestions and verified information, and presented in a simple way, the AIFA has decided to enrich is activity of institutional information by giving voice to the sick. The guide "I've Got Nothing To Lose By Trying It" brings together experiences of those who have encountered, unfortunately, false emissaries of hope and have suffered the consequences; it also indicates the most authoritative sources for information on the state of research and about the clinical trials of new medicines, conducted in accordance with scientific rigour.

7.1.c From the Di Bella method to Stamina: clarity above all

The freedom of choice of treatment presupposes that the treatment is genuine and scientifically tested. The AIFA not only strongly backs all initiatives that truly have the purpose of pro-

tecting citizens but praises the perfectly argued and scientifically justified position taken by the Regional Commission for the official Sicilian List of Therapeutic Medicines regarding the parliamentary bill of the Sicilian Region, according to which "it would be necessary to ensure the financial support of oncology patients treated with the 'Di Bella Method' who live in Sicily and are in conditions of financial difficulty."

Indeed, the AIFA is convinced that, even with respect for the decision-making independence of the individual institutions, the economic and cultural resources for health and pharmacological treatments must be invested in a rational way that is justified by medical evidence. The allocation of funds, which in the specific case could amount to 5 million euros, cannot and must not be influenced by emotional or media pressure that leaves the citizens, in this case precisely those in conditions of financial difficulty, prey to decisions that repudiate science to the utter detriment of the National or Regional Health Service.

The opinion expressed by the Regional Commission for the Official List of Medicines, in addition to being worthy of careful attention, must also prompt reflection on the dangerous tendency to simplify delicate issues, such as those that concern health, to the rank of disputes between supporters. Indeed, the Commission made clear that the cost of the treatment "is a pointless cost for the Sicilian Health System", that "there are no scientific reasons for which a doctor, in science and conscience, would prescribe a treatment like the Di Bella Method, not only ineffective but actually harmful for patients", but above all that "prescribing the Di Bella Method is harmful conduct with regard to patients."

This is pointless expense, therefore, that would be a burden on the NHS without producing benefits, without scientific validity, and that swindles patients. If history, as we like to think, teaches us something, it must be remembered that, at the height of public pressure, media attention and protests led the Ministry of Health to authorise, through an urgent measure, a "forced" phase 2 trial of the so-called Di Bella Method by the National Health Service, which deemed it ineffective.

Circumstances that sadly found an echo in recent reports of the Stamina affair. The AIFA also supports the Italian Pharmacological Society, which made known its views in its own Position Paper on the matter. The IPS, in its own words, "states its firm opposition to any form of treatment that does not meet the following prerequisites: - a strong pre-clinical, scientific rationale; - scrupulous characterisation of the active ingredients or cellular components that are administered; - a precise assessment of the risk/benefit ratio before every clinical trial; - the positive outcome of a blind, randomized controlled trial that, with its predictive value, demonstrates the scientific value of the treatment."

The Di Bella Method, however, notwithstanding the unanimity of the negative opinions expressed by all the competent authorities, succeeded in becoming the emblem of "freedom of treatment" in the worst sense of the phrase, that is, irresponsible, demagogic and misinformed.

A little while ago, the journalist Corrado Formigli, during the programme "TvTalk", said: "I took a personal interest in it, I was working with Santoro then. I interviewed Professor Di Bella, I made inquiries about the sick, I went to Modena to retrace the path of those suffering from cancer who made this journey of hope and expected to be received by Professor Di Bella. So we made several episodes asking whether there was freedom to experiment. And I must say, I am a little ashamed, I admit it, of having too easily accepted it, of falling into the trap of Di Bella's propaganda and was perhaps a bit hasty and superficial."

A significant *mea culpa* that underlines, on one hand, the difficulty of conveying complex content without falling into easy, and too often convenient, commonplaces and, on the other, the need to communicate science with rigour.

We like to think of freedom, whether of expression, the press or treatment, in terms of emancipation, progress, advancement; we think it is our duty to protect patients on the scientific level with rigour and discipline because medicine is in an empirical science that must, however, produce effective and reliable data and results. This protection also extends to the moral field because the credibility of the institutions is sometimes measured through decisions that, even though they may seem difficult to understand, are always taken to protect all citizens, without economic, social or geographical distinctions.

7.1.d Di Bella and Stamina: waste and illusions

When we published "From the Di Bella Method to Stamina: clarity above all" and the Guide for patients on "miracle cures", our intention was to draw the attention of public opinion to an affair that, many years later, is still the source of discussions.

The AIFA, faithful to the principle of national, unitary healthcare, which must be protected in its entirety, after having backed the opinion of the Regional Commission for the Sicilian List

of Therapeutic Medicines and the Position Paper of the IPS, now acknowledges, with satisfaction, the authoritative opinions expressed by the Regional Bioethics Committee, the Italian Board of Primary Oncological Hospital Doctors, Hepatologists and Gastroenterologists, in unanimous opposition to the parliamentary bill of the Sicilian Region, according to which "it would be necessary to ensure financial support for oncology patients treated with the 'Di Bella Method' living in Sicily, who are in conditions of financial difficulty."

The Regional Bioethics Committee, for example, found that "Di Bella's 'treatment' produced three serious negative consequences for many decades: it diverted patients susceptible to potentially effective treatments against cancer; it diverted resources for the treatment of pain and other symptoms from sick patients no longer susceptible to treatments against cancer; it caused financial waste to the cost of patients or public medicine that cannot be calculated but that is certainly considerable; damage that is even more severe in times of crisis and of the growing availability of treatments against cancer and effective palliatives."

In recent months, the AIFA has repeatedly stated the need to allocate resources, especially at a critical time like the present, to all those problems that afflict the sick and not to pay for a treatment that has been proved to be clearly ineffective.

It is well to remember that the recent data drawn up by OsMed showed that, compared to an agreed national average cost of 141.2 euros per head, a maximum value of 178.9 euros per head was recorded. It is therefore intuitive to understand that, before considering the allocation of funds for initiatives that have no therapeutic value, it would perhaps be appropriate to re-calibrate the existing costs for pharmaceutical assistance and direct economic commitments to interventions from which patients can really benefit.

The Italian Board of Primary Oncology Hospital Doctors (Collegio Italiano dei Primari Oncologi Medici Ospedalieri, CIPOMO) expressed its opposition to any legislative attempt to "dust off" the Di Bella Method but welcomed the opportunity to suggest some ideas on the best allocation of the finance requested, underlining "the problem of the new class of medicines identified as CNN (Class C Non Negotiated)" that "has created an unacceptable territorial disunity in access to the medicine, on the basis of the economic possibilities of every individual hospital, reaching the point, as absurd as possible, of starting to see in Italy what we would never have wanted to see, which is to say that the patient (wealthy) is forced to buy an efficacious and innovative medicine for the treatment of his or her illness." The sum of 5 million euros a year, CIPOMO suggested, could "be allocated to buying these extremely effective medicines, pending reimbursement." A second sector in need of interventions, the CIPOMO continues, is clinical research.

The Hematology Society then focused on additional detail of no lesser importance. "We are aware," they write in a note, "that there are patients who resort to the Di Bella treatment and we believe this is the result of the inadequate communication of the danger and damage of this treatment to all health operators and, above all, to general practitioners."

The Italian Association of Oncological Medicine of the Sicilian Region has sometimes given rise to concern, surprise and confusion due to the proposal to finance a method that has never been approved with new funds.
The position of Hepatologists and Gastroenterologists who work in Sicily was very firm: they stated in a note that "other, numerous forms of charlatanism infest the healthcare world, not only in Italy. In Italy and the rest of the world, useless remedies are sold every day at high prices that do not contain any active ingredient that has been validated with scientific criteria. The squalid odyssey of Stamina, with an embarrassing Via Crucis of media misinformation, international tomfoolery and courts that do not know how science works, has once again thrown into sharp relief the lack of all credibility and seen the emergence from the undergrowth of the dubious characters, graduates in medicine and otherwise, who lurk behind these pseudo-healthcare practices. In all these affairs of pseudoscience, plunder greased by desperation and media bungling, there is not even the mere veneer of the scientific nor a shred, even hazy and fragmented, of a theory on the physiopathological mechanisms."
The unanimity of these opinions leads us to an unavoidable considerable and a question to be put to the citizens, the real judges of the work of the institutions. Who is really on the side of the sick? Why was it decided to exploit physical and psychological pain? Why do Associations that claim to represent the sick so often adopt this role? Why are the institutions, doctors and scientists restricted to the role of heartless fire-eater?
"Our role as General Practitioners is very delicate," said Dr Saffi Giustini, "because when members of the public ask us for our opinion, we must be able to be clear but never banal, precise without being disagreeable. It is the duty of the State, the AIFA, doctors and the entire supply chain in general to provide the right medicine at the right time for the right reason. The real protection that can be given to the patient is the verification of the methods. Similarly, explaining the course of the life of a medicine is the only way, together with dialogue and understanding, to clarify the many doubts of patients."
The AIFA has witnessed, but also resisted, a continuous attempt to humble science, to mystify through the opinions expressed rather than argue on the basis of intellectual honesty and rigour. In this farce, in fact, the truth is mixed with the probable; everything becomes possible, every role takes on the features of the grotesque with the sole effect of confusing good and ill, what is right and what will never be so.
Both in the case of the Di Bella Method and, more recently, Stamina, the picture offered to the public was of institutions deaf to the clearly more virtuous calls of the father of a family, light years from the health needs expressed in favour of opportunistic and chameleonic television cameras.
During the hearings launched by the Senate Hygiene and Health Commission, Senator Elena Cattaneo made clear that the phrase "stem cells" immediately suggests a cure, almost

a miracle. The truth is that there are real studies on stem cells that are producing encouraging results. The results of a trial, however, come at the end of a process, sometimes very long, in which rules are fundamental. "The information organisations," Saffi Giustini remarked in this regard, " should also take responsibility for this aspect, which is less interesting from the media's point of view but would help people understand that science must not, for their own good, bury itself in the labyrinth of obscure, improvised treatments."

The former minister, Ferruccio Fazio, during the hearing of the Senate Hygiene and Health Commission into the Stamina case, underlined that the often wrongly cited phrase "compassionate treatments" was never used in the Turco-Fazio decree.

"The decree issued in December 2006," the former minister made clear, "refers specifically to a regulation that, in the interim, was approved by the European Parliament and therefore the whole terminology must refer to that of the European Community. I don't like the word compassionate either," and added that the reference must always be to "fully documented treatments."

Even the word "compassionate" has therefore been exploited in a linguistic dispute over what (or even worse who) is worthy of pity and what is cruel. In setting good against bad, virtue against evil, the only effect has been to create confusion and make the State appear to be a soulless organisation and members of the public the victims of foolish decisions. The real killer is, however, false hope.

"More education about health is required," explained Dr Saffi Giustini. "If we give people the knowledge, the fruit will be seen in the future because the young people and children of today will be the citizens of tomorrow. Therapies exist now that seemed utopian only a few years ago. This is where the progress of science lies, in assuring the condition of patients is improved."

"This kind of phenomena is also becoming more common," says Saffi Giustini, "because it is amplified to the utmost by the media" and Ferruccio Fazio also spoke of an "aggressive media." Communication once again to the fore, in short.

Toscana Medica, the monthly newsletter of the Doctors and Dentists Association of Florence, examined the Stamina case in-depth and, in one of the key passages, stated: "It is true that the boundary between medicine and charlatanism is sometimes uncertain in a science based on probability, aimed at acting on the most complex machine in existence, the human being. When medicine cannot solve the people's problems, 'miracle' cures always existed, exist now and will always exist. The witch doctor can often show the kind of empathy that is, these days, concealed behind the reductionism of technique."

If anyone thinks that Italy might be an Eldorado for pirates without scruples, we obstinately reiterate that our battle does not end here.

7.1.e Stamina case: the tricksters of hope found guilty

In recent weeks, the "Stamina case", however much its "inventors" might have wanted, has no longer filled the front pages of newspapers nor the running orders of news programmes or the TV talk shows, and has recently undergone an important stage in the process of its sad and deserved epilogue, but it cannot be archived and removed from the public consciousness of the country and the reflection of the scientific community and public institutions. Yet this is what we risk by collectively forgetting the bargaining with balladeers who trifle with the most devastating illness known to man and mislead the pain-filled hearts of the families of the children who were tragically struck by these terrible calamities.

So we remember. We remember that if the penalty is bargained over but not the crimes, to bargain is to admit full guilt. We remember that there can be no bargaining with the false hopes with which we have had to battle in the last three years in the knowledge we were defending, including against the mobilisation and exploitation of public opinion, the primacy of Science, Medicine and its rules, on which the true evolution of knowledge and, above all, the protection of public health depend.

We remember we are dealing with aggravated criminal association aimed at fraud that not only sold fake and faulty goods (because this is what was involved) but also the hope of a cure to those for whom it ended in tears. We remember the arrogance of the alleged healers and the media charlatans. Look at today's videos and the previous interviews; reread the statements, the blogs, the tweets and the Facebook profiles, if all those who published them have the gall to leave them online, just as they had the gall to contribute to deceiving so many families. Or perhaps they think it is enough to admit their guilt and, at a stroke, everything will be forgotten? We will not forget, we cannot. We owe it to the sick children and adults, all duped and used like emotional picklocks; we also owe it to the colleagues, scientific committees, the academic community and the other regulatory bodies that have helped us.

We also remember how, usually, the so-called gurus of alternative therapies (which are fine for alternative diseases but not real ones) at this point choose the shadows and, finally, the dark, rather than exposing what they orchestrated to the full light of day. They opt for the swiftest legal route (plea bargaining and fast-track proceedings) because this is entirely consistent with the behaviour of a lifetime: they always prefer the shortcut.

We remember that, in the name of alleged pseudo-cures, they even weakened the system of rules that ensure the rigour and transparency of scientific research that have, for more than a century, enabled clinical progress to be verified and assessed in accordance with agreed, standardised procedures, thereby protecting the health of members of the public and their right to have access to experimental treatments that are effective and safe.

This is why, beyond the judicial destiny of those at the centre of this tragic affair, which is of little interest, we wish to restate the necessity of developing antibodies to defend against similar threats in the future: a gradual process of immunisation that must take root at every level, involving policy, the law, ethics and information. The recent results of the extensive investigation by the Senate Health Commission are also useful for this and are available to all.

We remember that the AIFA, from the beginning, strictly adhered to proper conduct, even when the winds blew against us, and they were the winds of a powerful storm. From the first quarter of 2012, aided only by the health and medicinal adulteration section of the carabinieri and as requested by the Turin Public Prosecutor, we immediately confirmed the inconsistency and potential danger of the Stamina method, prohibiting, by decree, further infusions at Brescia public hospital. With transparency and consistency, we subsequently provided technical and scientific support on the issue to the government, parliament and judiciary and defended, including through the release of accurate information, scientific reasoning against all attempts at deregulation and delegitimisation of the system, with the sole guiding principle, as always, of the interest of patients.

It is well known that the AIFA is committed, like other agencies throughout the world, with the same resolution, to promote advanced Research, with a capital R, conducted in accordance with the rules and so able to provide scientific evidence. On this basis, a Ministerial Decree has just been enacted by Minister Lorenzin, which will regulate advanced therapies in our country from now on.

In Europe and around the world, the AIFA is actively contributing to the definition of fast-track trials and new authorisation models that enable patients to swiftly benefit from promising treatments, while ensuring, at all stages, the careful and scrupulous monitoring of quality, effectiveness and safety. This is because there are still many unsatisfied health needs to which researchers must try to find responses. We are working quickly to overcome the boundaries of knowledge and provide medicine with new and more effective tools to combat diseases that are currently still incurable.

We also remember those, in addition to the sick and their families, for whom we must do everything we can to avoid the germination of other "Stamina cases", fed by the bad faith of some, the ingenuity of others and the media speculation that so easily flourishes where life and death are in play. For all these reasons, we cannot forget and we are against any form of bargaining with our memories. Judgements, including in eyes of the layman, must always have educational value, never an instrument of vendetta but inflexible instruments against unacceptable trickery.

As the Public Prosecutor Raffaele Guariniello said, Justice, in this case, also helped Science to stand up for itself and its rights. The judge imposed thirteen sentences for as many charges without any acquittals, entirely confirming the proof gathered by the investigation and the

prosecution case. Do those condemned now want us to believe they were only kidding because they plea-bargained? Let us remember, then, that you don't kid around with people who use hope to deceive the most noble sentiments of an entire country.

7.1.f The AIFA on the Stamina ruling: "only scientific verification can establish the validity of treatments"

The AIFA makes known its satisfaction at reading the reasoning behind the ruling of the Constitutional Court that finally put an end to the sad affair know as the "Stamina case." With its incontrovertible ruling, the Court indeed reaffirmed what it had already stated at the time of the "Di Bella" affair and subsequently repeated regarding the necessity for therapeutic choices to have been scientifically tested and validated in advance, as strenuously argued by the AIFA. These are principles that, in the past two and a half years following the AIFA Decree of May 2012, seemed to have been forgotten by the many magistrates who ordered Brescia hospitals to carry out treatments based on the seductive and secret "Stamina method".

The Court confirmed that it is only after scientific verification, which produces confirmation of the efficacy and validity of a treatment or a medicine, in accordance with national and international regulatory procedures, that the National Health Service can be called upon to shoulder the respective cost.

In this ruling, the Court affirms even more clearly that "the drawing up of guidelines founded on the verification of the state of scientific knowledge and the experimental evidence acquired" must be carried out "through dedicated institutions and bodies – national and supranational – given the vital importance of the technical-scientific bodies for these purposes" and cannot arise from the political choices of the legislature. The Council then unequivocally acknowledged the vital role of the institutions and bodies assigned to carry out the institutional tasks of a technical and scientific nature, including the AIFA and the ISS, inviting the legislature and, implicitly, judges, not to enter into spheres that require in-depth scientific knowledge with "judgements of a purely political nature."

Moreover, the promotion of a clinical trial to test the efficacy, and exclude the harmful side effects, of a new medicine does not, as a rule, impose in advance the responsibility for public facilities to administer that medicine; this is for obvious reasons of protecting health, as well as the requirement of the proper use and allocation of the funds and resources available to the National Health Service.

The Agency, in addition to recalling its own tireless commitment to avoiding the use of these treatments devoid of any scientific justification, underlines that it has been possible to defeat

this fraudulent phenomenon only thanks to the joint commitment of the institutions assigned to protect public health, the health and medicines adulteration carabinieri unit of the Health Ministry and especially Minister Lorenzin in person who, from the start of his term in office, worked to tackle the question with a scientific and not an emotional approach, supporting the constant and thorough work of all of us, through the tireless efforts of illustrious exponents from the Italian scientific and intellectual world, such as Elena Cattaneo, Paolo Bianco, Gilberto Corbellini and Michele De Luca, who personally became involved. The work of the investigation launched by the Senate of the Italian Republic, thanks to the action of Elena Cattaneo, this time in the role of lifetime senator, jointly with Senator d'Ambrosio Lettieri and under the presidency of Senator De Biasi, was also fundamental. The Agency also acknowledges the ceaseless work of the Turin Public Prosecutor and a number of judges who understood from the start the real interests that fuelled the affair and that, unfortunately, never intended to cure unfortunate people suffering from diseases that are still incurable.

7.1.g The European Court of Human Rights has laid down that scientific evidence must support compassionate treatments

The European Court of Human Rights has laid down, through a judgement issued recently, that patients do not have the right to automatically have access to a compassionate treatment unless supported by scientific evidence.
The European Court ruled in this way in rejecting the appeal of an Italian citizen whose daughter suffered from a degenerative brain disease since adolescence. The parent appealed to the Court after the Court of Udine rejected his application to give his daughter access to the so-called "Stamina method." This ruling was, according to the appellant, detrimental to the right to life and also discriminatory since, in cases similar to his daughter's, other Italian courts had authorised access to the treatment. The European Court rejected the Italian citizen's appeal, stating that the prohibition against the patient undergoing the "Stamina method" imposed by the court was pursuant to the legitimate aim of protecting health and was proportionate for that purpose. The judges laid down that the case had been properly considered and that the ruling had been duly justified and not arbitrary. According to the European Court, then, the patient was not at all subject to discrimination, even if some Italian courts had allowed the same treatment for similar diseases.
As is shown by *Bio Law Journal – Magazine of BioLaw*, published online by the Faculty of Law of the Universities of Ferrara, Naples and Trento, "the Court grants States a wide margin of discretion when dealing with access to compassionate treatments by people suffering from serious illnesses and highlights that, in the actual cases, the scientific value of the treat-

ments in question could not in any way be said to have been proven. It would not therefore be the task of an international judge to replace the competent national authorities in determining the acceptable risk for patients who seek access to compassionate treatments in the case of experimental therapy, the efficacy of which has not been proven."
The ruling of the European Court of Human Rights was welcomed by the international scientific community, which had always followed developments in the case very closely. In this regard, in a post on *Nature*'s blog published on 30 May 2014, Alison Abbott, who followed the affair from the start, praised the work of the Court and spoke of a "historic" ruling. Indeed, in Abbott's opinion, the ruling can be a guide for all judges who have to deal with the applications of desperate patients searching for unproven therapies, promoted outside the regulated medical sector. At the end of the remarks, Abbott quoted the words of the German lawyer, Clara Sattler de Sousa e Brito, an expert in biomedical law, saying that this clear ruling on the necessity for scientific proof will help avoid recourse to unproven therapies for so-called compassionate uses in the future.
The ruling of the European Court of Human Rights is further acknowledgement of the validity of the work of the AIFA. The AIFA was created to ensure access to medicines and their safe and appropriate use as an instrument for the protection and promotion of health, and works with the sole aim of protecting the health of the citizens. It is precisely to attain this end that the Agency ordered the suspension in May 2012 of adminstrations based on stem cells by the Stamina Foundation at Brescia public hospital due to failure to comply with the regulations for safeguarding the health of patients.

7.1.h Why we failed to stop Stamina at once

Every so often, in the life of a man, there are days that stand out from all the others.
For me, the most recent was when I found out that a child of three and a half had been given an injection of the so-called Stamina method, in the spine with a needle that, due to its size and the lack of anaesthetic, certainly did him harm. I felt then that I had failed. I have been a doctor for thirty years and I swore a sacred oath, the same oath that has been sworn for 25 centuries, that commits us to defending human life, all human life, not only the person in front of us. I did not know the patient in this case, I had never even seen him in person, as may have happened with any of my colleagues, but I felt responsible for him. Even if his family does not want me even to name him.
If I could not prevent this "unlawful" and dangerous act through a decree, the most forceful action that the AIFA can ever take, I wondered what purpose my mandate really served. I became very preoccupied and, out of bitterness and pain, I sent a message to Minister

Lorenzin, who I was convinced would understand. Then I did not answer the phone for a very long time. This had never happened to me.
In the silence of a very long walk, I asked myself how I would be able to continue to carry out my duties, for which I must answer as a doctor, and those that bind me in loyalty and through membership of the institutions I represent. I asked myself what was the point of being the Director General of the AIFA. A position of "power" that is, in the collective imagination, much sought-after. It is a pity that I was never interested in power. The "power" of a doctor is entirely concentrated in curing the sick, but if he cannot even prevent a defenceless child being harmed, what power does he have? Who are you? It was like failing twice.
The appointment of Andolina as assistant to the Court of Pesaro, which, in fact, placed him in a position to treat patients, breaks all the national and international rules on every kind of treatment, breaches the doctor-patient relationship, goes against the code of ethics (even the new one), against the regulations of public and/or private hospitals, against the guidelines, against all and every code of ethics and conduct that are the foundation not only of medicine and healthcare, but also human life, as the European Court of Human Rights has recently stated.
Someone else who knows nothing of science and medicine ordered the liberal dissemination of a secret, which is not a cure, nor a therapy, nor even a treatment. Something is being disseminated that we do not even know how to define, and all this leaves us speechless. At least it does me.
Many years have now passed since the decree by which we in the AIFA and the health and the Carabinieri special unit called NAS precisely defined the violations committed by Stamina. A decree that always remains valid, even when applied, or worse, misapplied by judges with a rationale that is impossible to understand. Why?
Because medicine, in this case and increasingly often, is no longer in the hands of doctors, who are committed to answering, as always, only to science and conscience, and so are responsible for what they do. The temple of medicine is the sickbed and the places the profession is practiced are the corridors of hospitals, not those of courts. This new practice, which is certainly not science, clinical practice and still less art, is currently been smuggled in by jobbing charlatans, tricksters and impressarios who are not even a businessmen, nor do they feel the need to have graduated in Medicine in order to call themselves Doctors. In Italy, there is, of course, never any lack of help from the accommodating politician who, to grab the limelight and ninety seconds of glory on the national television news, will not hesitate to sell the conscience they lost some time ago to the highest bidder. And even acknowledging that the decisions of judges must be respected (just as the laws of parliament should be respected), I wonder whether the person who actually creates the circumstance where an assistant is put in a position to carry out a prohibited activity, and who orders this type of administration, knows precisely what he has done. I hope not.

It is known, then, that regulatory agencies like the AIFA around the world are working to ensure that the Therapies, with a capital T, that have been widely described in this book arrive with the utmost degree of priority and safety for people suffering from very serious diseases. Pathways exist for fast-track experimentation, preferential lanes that we have created in Europe and, for this reason, we cannot accept and tolerate uncontrolled or instrumental deregulation to make the financial budgets balance on the backs of patients. In recent weeks, I have had the distinct sensation that this is precisely the direction in which we are heading, due also to the uncontrolled bombardment of false information that has raised unfounded hopes in those in the tragic situation of suffering from diseases that, currently, cannot be cured. So I asked myself why, in the face of these expectations and so much desperation, many others have refused to supervise or intervene or found it impossible to do so. I believe the reason is precisely what has got under my skin: all of this can be very painful, given the many interests in play that have nothing to do with the sick and with medicine. And so there are those who prefer to close one eye, or both, and leave things as they are. But no one remains forever invisible to the eyes of History.

History will soon raise the curtain on a new world that I was reluctantly obliged to discover, made up of aggression, insults, slander, threats and intimidation that incite hatred against a diametrically opposed way of seeing life and the profession. They hate science, the rules, the discipline but also the effort, the sacrifice, the humility and the sweat. They bend the laws to their interests and change them to the detriment of patients. It's not for me. This carnival of ignorance, which seeks to drag everyone into the mud to make us pliable and complicit in a non-culture that is incoherent and vague and feeds on conceit and arrogance, leaves a bitter taste that cannot be endured.

I no longer recognise the pillars of medicine that I studied and that I love, which explain how to discover and really study diseases, medicines and treatments but I do see boundless space given over to extreme superficiality and intense media marketing campaigns entirely devoid of real substance.

At the end of that extraordinary day, I realised that these attacks also had (and still have) the aim of dragging the rigorous and ethical framework that guides the existence of most scientists and doctors into a grotesque pantomime of triviality and gratuitous malice. I see the ideals for which I chose my profession trampled down and insulted and I ask myself if there is still a modicum of hope in this country, and whether there is still any room for those like me.

7.1.i Stem cells as the key to weakening the regulatory system – Bianco and Sipp in *Nature*

The AIFA was delighted to read in *Nature* an article by Paolo Bianco[72] and Douglas Sipp, who describe and present with clarity what was also suspected by the AIFA in the last two and a half years. Bianco and Sipp precisely demonstrate the existence of a transnational movement that seeks to overturn the fundamental rules that are at the basis of the approval processes of medicines in advanced countries, that is, the mandatory demonstration of evidence of the efficacy and safety as conditions for the release on the market of any therapy.

Bianco and Sipp warn against these new financial enterprises built on human suffering that, as a result of shifts of entirely misinformed and often incompetent opinion, hoist the banner of "freedom of choice" to focus on the release of alleged treatments on the market at an early stage, without any demonstration of safety and efficacy. The "Free to Choose Medicine" campaign launched by the Conservative think tank "Heartland Institute" in 2010, according to the authors, was the first clear attempt at deregulation that would have allowed the industry to release medicines on the market following clinical trials reduced to the minimum, along with guarantees for patients.

The language and tone of this proposal can been seen, according to the authors, in other proposed legislation and even in the words of a former Commissioner of the *Food and Drug Administration*, Andrew von Eschenbach who, in *The Wall Street Journal* looked forward to the creation of a "fast track" for regenerative medicinal products that would have put them in pharmacies immediately after toxicity controls, postponing the efficacy and safety tests until the *post-marketing* stage.

Bianco and Sipp also recall the very recent legal battles that set the FDA against a number of companies that marketed products based on autologous stem cells. The principle (always losing) unfurled in the precincts of the courts by companies like Celltex Therapeutics and Regeneration Sciences was that stem cells, extracted from a patient and reimplanted in the same patient following manipulation, were not medicines and therefore did not require regulatory approval. A very dangerous interpretation that is taking hold in a number of countries in the world, even in Australia and Japan, due to enormous commercial and political pressure. The approval of rather lax laws has turned into an advertisement for medical tourism, an extreme form of a journey of hope that appeals to the sick from every part of the globe in the search for a remedy to the abyss created by the lack of alternatives.

[72] On the morning of 7 November 2015, a mutual friend, Gilberto Corbellini, called me to tell me that Prof. Bianco had left us. Paolo was a scholar in stem cells and the physiopathology of the skeleton of worldwide renown, a lecturer at La Sapienza, anatomic pathologist, direct of the anatomic pathology unit of the Polyclinic of Rome, one of the most intelligent and competent people I have ever met in my life. I learned more from him in a few years than hundreds of lessons by all the others.

The *raison d'être* of clinical trials, according to the two authors, is, however, that they are the only guarantee of efficacy and safety for patients. "Simply the idea of putting products on sale," Bianco and Sipp write, " and in the bodies of consumers on the basis of phase 1 data is troubling."

The premature marketing of therapeutic products that have only passed through phase 1 would expose patients to unnecessary and potentially serious risks.

By shifting the focus of operations from the regulatory bodies to the patients themselves, many "clinics of hope" convince desperate people to sponsor so-called experiments on themselves that have little or nothing to do with science. The appeal to freedom of choice and the cry of pain against "bureaucracy" form a smokescreen designed to conceal this new business model.

So what is the right way forward? Bianco and Sipp illustrate the route to market followed by the first gene therapy in Europe, *Glybera* (alipogene tiparvovec). The medicine was released onto the market to treat a potentially fatal form of pancreatitis, an extremely rare disease. In arguing for approval of *Glybera*, due to the limited number of patients, the amount of data presented was much less than usual. After a long discussion, due to the Italian representatives (Daniela Melchiorri and Luca Pani) taking a different view at the CHMP of the European Medicines Agency (EMA), *Glybera* was authorised, on the indispensable and binding condition, however, of very close monitoring of the efficacy and safety data.

As in the case of *Glybera*, the authors conclude, regulatory agencies, researchers, governments and companies must find innovative solutions that enable the potential of regenerative medicine to be made available to patients and so keep the merchants of false hope at bay.

7.1.l Cattaneo and Corbellini in *Nature*: taking positions against pseudoscience

The first email from the Directorate General of the AIFA to Professor Elena Cattaneo was dated 29 March 2013 and began as follows::

Hello Elena,
I have been in the swamp that comes from the eclipse of reason, from 16 May 2012 until now. No one has helped me. The kindest words I heard were: "What are you thinking about? Who do you think you are? Why are you making all this fuss? What does Stamina matter to you?" [...]

In an article published in *Nature*, the scientist and life Senator, an expert in stem cells at the State University of Milan, and Gilbero Corbellini, historian of medicine at the Sapienza University of Rome, retraced the stages of the battle against Stamina and shared their experience, sacrifice and efforts to support the cause. "Desperate patients are always vulnerable to exploitation. We hope that by sharing our experience we can help other researchers to join us in the fight against predatory pseudoscience."
The two academics relate that, from the winter of 2012, a few months after the restraining decree of the AIFA, together with the other scientists involved, they began to realise what was really happening and started to alert patients, politicians and the press, writing articles and giving dozens of interviews every week to confirm that the Stamina method was lacking scientific evidence. Sleepless nights spent searching websites and Facebook pages together with other scientists, such as Michele De Luca and, above all, Paolo Bianco, in order to find out how the Fondazione Stamina, which was presented as a private charitable organisation, had the same address as Medestea, a commercial company that had been fined for misleading advertising of food supplements.
"The last 18 months have been a roller coaster of hope, disappointment, triumph and indignation," write Cattaneo and Corbellini. "We scientists have spent hours and hours speaking to politicians by phone, in person and by video conference. We prepared and provided at least six dossiers containing dozens of pages and scores of slides. We gave interviews to journalists and wrote articles almost weekly. We exchanged letters and comments with patient organisations; we established relations with doctors at the public hospital that hosted Stamina, by then distanced from Vannoni." The two scientists tell of the numerous requests from student associations, university professors, organisers of scientific conventions, patient associations and other groups to speak about the Stamina case. "We have never held back. We estimate

that every one of us has so far given up between 60-80 weeks of work in the laboratory."
"Some of us," the scientists continue, "have even received threatening letters and insults from people who believe we feel no compassion over the deaths of patients; our Universities have been the targets of email blitzes and other digital attacks."
The AIFA has been continuously engaged in the Stamina affair, arguing and defending, often in arenas that ought to have recognised its expertise and authority, its work. In all this, the contributions of a number of Italian scientists have been fundamental to fighting this battle to protect respect for the rules, legality and the extremely fragile and defenceless health of patients. Similarly, the backing of the international scientific community was, for Elena Cattaneo and Gilberto Corbellini, very precious. The support given by the International Society for Stem Cell Research to Cattaneo, Bianco and De Luca reinforced the credibility of these scientists in Italy and abroad. Here too, finding the right allies and getting the best from them was fundamental: "We must be able to speak to everyone, irrespective of scientific knowledge, from taxi drivers to lawyers. Cultivating relations with the scientific colleagues involved in the battle was also fundamental. We have had to learn to be generous and remember that we share a single objective; maintaining political actions and disseminating valid and effective communications require a united front."
A series of sacrifices in the name of science and knowledge, then. "But it was worth it," conclude Cattaneo and Corbellini. "Now, following the ruling of the European Court of Human rights and the Senate investigation into the case, we are confident that these dubious treatments will soon be banned in Italy; they had already been banished from Switzerland in 2011 and Cape Verde at the start of this year. We urge all scientists to fight for the scientific method. Science depends on the public institutions and is conducted in the public interest: it is our duty to defend both."

7.1.m Stamina Case: news of a decision foretold

The Stamina method "cannot be tested due to the absence of scientific presuppositions." Two (!) Scientific committees of experts appointed by the Ministry of Health, a parliamentary inquiry, hundreds of hearings in courts throughout the country, three years of legal disputes and media battles fought on the backs of the sick and their families were all needed to establish that. Conflicts that have risked shattering what little culture and scientific credibility still exists in the country that, long, long ago, was the birthplace of Galileo.
Even though it had already all been written down in black and white, back on May 16, 2012. In the decree of the AIFA, the first issued in its history, a list is given of a series of very serious violations that, looked at again in the light of everything that happened, leave no room for interpretations.

In any advanced western country, the few pages of this decree would have been enough to lead to the cessation of any activity. The decree bore witness to the results of a joint inspection with the Carabinieri special unit called NAS, carried out on the precise request of the Judicial Authorities, and contained many critical points. We listed them all: the non-GMP characteristics of the laboratories, the processing of biological material by two collaborators of a Foundation, without any protocol to certify the rationale and the methodology. Thirty months ago, we certified that doctors who inoculated the "preparation" obtained by this secret method did not know the content of what they were injecting into their patients, clearly breaching the rules of professional ethics (which prohibits the use of secret methods), as they themselves admitted.

It is disconcerting to read those four pages again and think that, only a few months after the prohibition ordered by the sole competent regulatory agency, numerous courts accepted the appeals presented by the families of patients, without ever consulting us, ordering the "treatments" at Brescia public hospitals to resume.

The Stamina affair also invaded the political sphere the following year with the promulgation, on March 25, 2013, of the so-called "Balduzzi Decree" that allowed the treatments to continue "on individual patients with medicines for advanced therapies based on mesenchymal stem cells." This law could have turned into a Trojan horse capable of destroying the current rules throughout the European Union and turn Italy into a free port for the "merchants of hope."

The credit for having averted this prospect, which would have relegated us to the margins of the international community, lies entirely with the voices of the scientists raised against the pro-Stamina campaign, who won followers in the media and among public opinion.

Paolo Bianco, Elena Cattaneo, Gilberto Corbellini, Michele De Luca and Giuseppe Remuzzi often stood up publicly to plead the cause of Science, to warn of the abyss into which we risked slipping without even realising it. But great credit, perhaps not acknowledged widely enough, goes to the best Health Minister that Italy has ever had. Appointed to the post on May 1, 2013, around three weeks from the enactment of the disastrous Decree that would have allowed fraudulent treatments to go ahead, she called an urgent meeting on treatments with stem cells that do not meet the prerequisites laid down by the current regulations and associated problems. At that meeting, the factual and legal aspects that characterise the Stamina affair were lucidly enumerated by Minister Beatrice Lorenzin, marked by the production and improper use of medicinal therapies based on so-called mesenchymal stem cells. With speed and "political" expertise to which we were not accustomed, the Minister took on board the doubts expressed by the Italian and international scientific community about the so-called Stamina method and, above all, was the first to understand the risks that would be run if this phenomenon were allowed to spread. And she engaged in a battle without quarter in the Chamber of Deputies and the Senate.

I am certain that it was due to this work of persuasion by Beatrice Lorenzin that parliament

introduced certain corrections to the measure and ordered that the treatments already begun could only proceed on condition that they were conducted "in laboratories of public facilities and in accordance with procedures suitable for the processing and preservation of tissue". It was also decided to start a clinical trial from July 1, 2013, coordinated by the Higher Health Institute.

This first Committee, called upon to assess the documentation and enable the start of a trial of the alleged method, of which I had the honour of being a member, was able to be certain about an organisation marked by reticence, delays and bombastic advertising never matched by reality.

The decision, taken in September 2013, was not to give a green light to the trial authorised by parliament, due to the lack of a solid scientific basis (which is certainly reminiscent of something).

Incredibly, it would once again be a judge who overturned the decisions of the scientists. The Lazio Regional Administrative Court in December 2013 claimed members of the Committee were partial and ordered a second panel of experts to be formed.

Another year was required to obtain an absolutely speculative evaluation, it has been learned, by the second Committee. In the meantime, twelve committals for trial were prepared by the Turin Public Prosecutor citing, among others, Vannoni and Andolina. The accusation of criminal conspiracy led to the process to which we referred in previous paragraphs, which helped clarify the criminal acts behind an obscure affair that, it is worth remembering, is still in many ways "an open case."

Now the sentences have been made final, the implications of the "Stamina case", which shone a light, as often remembered publicly by Minister Lorenzin, on various institutional short circuits are very clear. The snapshot of Italy that emerges from the past, almost four years, is certainly not comforting. The field of Science must, by definition, be the exclusive domain of method and evidence, while that of medicine must be centred on professional ethics and the sacrosanct nature of the "doctor-patient" relationship.

The right to the protection of health cannot and must not be the proverbial rug being pulled away from all sides. It is the institutional mission of the technical bodies to protect health and their decisions should therefore be protected from any interference.

In recent years, we have observed the systematic violation by many parties of the codes of conduct that are the common heritage of an advanced society. We are still in time to take stock and restore order by settling the cultural conflicts that have been created.

Our responsibility to those who are suffering is to avoid events like these ever happening again.

7.2 Not only Stamina: Mickey Mouse, ideology and measles

"Olivia, my eldest daughter, caught measles when she was seven years old. As the illness took its usual course I can remember reading to her often in bed and not feeling particularly alarmed about it. Then one morning, when she was well on the road to recovery, I was sitting on her bed showing her how to fashion little animals out of coloured pipe cleaners and, when it came to her turn to make one herself, I noticed that her fingers and her mind were not working together and she couldn't do anything.
- "Are you feeling alright?" I asked her.
- "I feel all sleepy," she answered.
In an hour, she was unconscious. In twelve hours she was dead."

This is how, in 1986, the children's author, Roald Dahl, described, with startling honesty, the disease that led to the death, in November 1962, of his beloved daughter Olivia, in a brochure produced by the UK's *Sandwell Health Authority* to explain to parents why it was important to vaccinate their children.
Olivia died from encephalitis, a rare complication (1 in 1,000) of the measles, against which modern medicine is still completely impotent, even today. The only weapon is preventive vaccination.
More than fifty years later, a measles epidemic is underway in the most powerful and developed country in the world, the United States, where more than 121 cases have been reported in 17 states in recent months, most of which are connected to an outbreak that began in the Disneyland amusement park in California. Yet, only 15 years ago, the Center for Disease Control and Prevention (CDC) declared that endemic measles, rubella and congenital rubella syndrome had been eradicated.
There is only one explanation for what is happening across the ocean, the return of measles is connected to the ever-increasing percentage of irresponsible parents who refuse to have their children immunised because of objections based on ideologies of various types. The result can be seen by everyone. In 2014, 644 cases of measles were reported in the United States, the highest number recorded in the last two decades, most of which concerned unvaccinated subjects (55%) or those whose vaccination status was unknown (31%), making a total of more than 85%.
More generally, all diseases that can be prevented by vaccination (for example, diphtheria, whooping cough, tetanus, measles, mumps and rubella [MMR]) are on the rise, including

in our own country, unfortunately, and various groups of parents are choosing to delay vaccination, selectively immunising their children and, sometimes, not vaccinating them at all.

The reasons behind this type of choice vary: fear of adverse effects in healthy children (even though numerous studies and independent reviews have found no link between the MMR vaccine and autism, concerns have not entirely been removed), the right to choose on behalf of their children, informed consent and even freedom of religion and conscience. A small proportion of parents are categorically opposed to vaccination and, given that it is known that irrational minds cannot be convinced by logical and rational arguments, it would be necessary to more precisely and more broadly inform at least those who are worried.

The new measles epidemic has rekindled a historic dispute over the enduring values of public health, freedom of personal choice and parents' rights. In a recent editorial published in *JAMA*, Lawrence O. Gostin of the O'Neill Institute for National and Global Health Law (Georgetown University, Washington DC) analyses the causes for this and provides interesting points of consideration for a regulatory agency like the AIFA.

In this matter, the right of each citizen to independently make decisions concerning their health and that of their children is set against that of the collectivity to preserve the advantages, in terms of prevention, gained through decades of mass vaccination. In addition to this, there is the growing resentment of those who, in the name of self-determination, risk compromising the so-called "herd effect", thwarting efforts at global immunisation and so putting everyone's health in jeopardy.

The media attention stirred up by the fact that dozens of unvaccinated children were struck at the same time in an amusement part like Disneyland in California that is famous around the world caused a reaction against their parents, who are now accused of undermining the protection of public health by their behaviour.

Although vaccination policy is often the source of division, the scientific community, Gostin recalls, is unanimous in considering that vaccines for children are safe and effective and are one of the great conquests of the 20th century. It is estimated that childhood vaccinations prevented more than 100 million cases of serious diseases between 1924 and 2012, with very rare adverse reactions.

These data bring to mind the words historically attributed to Daniel Patrick Moynihan: "Everyone has the right to their own opinion, but not their own facts."

The facts are the following: if the right of an individual reaches the point of threatening the safety of others, is it correct for different States to allow parents to remove their children from vaccination? The current "generous" system of theoretical exemption makes it possible for the breeding grounds of infectious disease to continue, intensify and expand. Nearly all American States, in fact, grant exemptions to people who object to vaccination due to religious ide-

ologies. Twenty States allow "philosophical" exemptions for those who object to vaccination on the grounds of personal, moral or other personal convictions.
These differences in approach of the American federation make unimaginable paradoxes possible. While California, the State with the highest GDP, struggles with the return of infection, Mississippi, one of the poorest States and known for the fragility of its health system (it has the highest infant mortality rate in the United States), launched a widespread vaccination campaign in nurseries, immunising 99.7 per cent of children. The result? Today, Mississippi is "measles-free."
What we find most interesting is that the trend in anti-vaccination behaviour both on the individual and regional levels is starting to display an inverse ratio to the rate of education and literacy of the general population. Many "white-collar workers", professionals and graduates refuse to vaccinate their children. These aspects of the American debate should also give rise to reflection by Europeans and, in particular, we Italians, where vaccination for measles has been associated with measles by a court.
These same factors that have primed the anti-vaccination movement in the United States could dangerously take hold in Europe, reopening a front that had seemed on the point of victory: indeed, 2015 was the year set by the European Regional Commission of the World Health Organisation (WHO) in 2010 for the eradication of measles, rubella and congenital rubella, which was deemed to be a priority objective of public health for Europe and Italy (National Plan for the Elimination of Measles and congenital Rubella 2010-2015, [PNEMoRc] 2010-2015) which, at this point, will be impossible to attain.
The most recent data do not appear at all reassuring. During the meeting of the WHO's ETAGE (*European Technical Advisory Group of Experts on Immunisation*), which was held on January 30, 2015 in Copenhagen, it emerged that the objectives of vaccination coverage (VC) required for elimination (≥95% of the population) had not been reached in many countries (including Italy). In Italy, the VC for the first dose of measles vaccine (MPR) in children aged 24 months in 2013 (2011 cohort) was around 90% and we fear that the results in subsequent years may be even worse, presumably with significant regional differences.
According to the European Centre for Disease Control (ECDC), 3,840 cases of measles were reported between December 2013 to November 2014 by 30 member States of the EU/EEA (65% of which were confirmed in the laboratory). Italy is the country with the greatest number and the highest rate of reports (n = 1,921, that is 32.2 cases per million inhabitants), followed by Germany (n = 348), France (n = 269) and the Netherlands (n = 250).
The national data confirm that measles still has a high impact on health. Vaccination coverage for MPR is not optimal and so there are pockets of people susceptible to measles, especially adolescents and young adults. In 2014, according to the integrated measles and rubella monitoring system of the Higher Health Institute, 1,674 cases of measles were reported. The rate of measles cases in 2014 was equal to 2.8 cases per 100,000 inhabitants.

Of these case, 58% occurred in the 15-39 age group (average age, 23 years) demonstrating that, in addition to the inadequacy of the VC for young children, there are population groups in our country that are susceptible to measles in the adolescent and adult age groups. To achieve elimination, therefore, the Higher Health Institute underlines in its Report, it will be necessary not only to improve the VC for young children, but also to vaccinate these other age groups, including through special immunisation campaigns. Reading these data imposes the imperative of not lowering our guard and not underestimating the effects of the new anti-vaccination ideologies that are emerging, which threaten to captivate the population.

The higher the number of parents who decide not to vaccinate their children, no doubt in good faith and, in certain cases, driven by fear and objections that must be understood, the greater is the jeopardy to the enormous social benefit we have gained through mass immunisation.

We are at risk of finding ourselves in what Garrett Hardin, in an article published in Science in 1968, described as the tragedy of common property.

Like the users of free pasturing in Hardin's example, mothers and fathers plagued by doubts and frightened by fraudulent data react by maximising individual interest and freedom. But the real danger concealed from them is the false perception that the common good (health) is unlimited and always constant.

If individual choice continues to be given preference over the interests of the collective, we will soon reach a critical threshold beyond which, as History teaches us, lies only the failure of the social contract and the reappearance of very powerful enemies that we thought we had defeated a long time ago.

Measles is one of them.