

# The Various Shapes of Innovation

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**Abstract: Background:** Innovation is one of the most difficult words to define, especially when it comes to health technology. The aim of this article is to get a better understanding of the multi-dimensional facet of innovation, how this is valued by different stakeholders and the way forward in order to create innovative interventions for the sake of the patients and the society.

**Methods:** A literature search was performed using mainly the PubMed database and reports from various organisations (EFPIA, etc.).

**Results:** In the past, innovation in the pharmaceutical industry was the result of the findings of basic science translated into clinical compounds, ending up in marketed drugs. This model is not valid anymore since significant changes reshaped the drivers of innovations and the key players. Rising costs, increased competition, new scientific and technological developments, well-informed patients created a much more challenging environment where coordinated and committed collaboration seemed to be the only way to overcome these obstacles and reach innovation in order to discover, develop and deliver medicines to patients.

**Conclusions:** Innovation initiatives have already proved their value by providing solutions to the major challenges the industry faces. It is now clear that a healthy biomedical ecosystem is determined by all stakeholders- academia, nonprofit/ for-profit research institutions, government agencies, pharma/biotech industry and patients. Innovation initiatives provide the platform needed in which all stakeholders can meet and share their knowledge in order to deliver through innovation improved outcomes for patients while shaping an efficient and sustainable healthcare system.

**Keywords:** *Innovation • Personalised medicine • IMI • MAPPs • Horizon 2020*

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## Introduction

Innovation is one of the most difficult words to define, especially when it comes to health technology, and a field for discussion and research that is inexhaustible. The aim of this article is to get a better understanding of the multi-dimensional facet of innovation, how this is valued by different stakeholders and the way forward in order to create innovative interventions for the sake of the patients and the society and not for the sake of innovation.

The Advisory Committee on Measuring Innovation in the 21st Century Economy defined innovation as ‘the design, invention, development and/or implementation of new or altered products, services, processes, systems, organisational structures, or business models for the purpose of creating new value for customers and financial returns for the firm’. (1)

In the literature, when investigating the definition of health care innovation, six different aspects can be found: benefit to the patient, therapeutic value to the health care system, something new/novel, new mode of administration, lower price and addressing an unmet medical need. In general, we can distinguish three main categories of innovation:

- Something new/novel
- The (added) benefit a drug delivers to the patient or healthcare system, and
- Something that delivers benefits (2)

Nevertheless, the objective is to define innovation given the current situation in a way that it reflects the future options.

Pharmaceutical innovation ranges from breakthrough treatments for life-threatening diseases to minor modifications of drugs that have been on the market for

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some time. Kristopher Hult, in his article 'Incremental Innovation and Pharmaceutical Productivity' (3), refers to incremental innovation that is an overlooked, but increasingly important, component of pharmaceutical innovation. There are two types of FDA-approved pharmaceutical innovation:

- Novel innovations, referring to the new molecules and
- Incremental innovations, referring to the new drugs created by modifying existing molecules.

Incremental innovations represent a growing share of pharmaceutical innovation and utilisation by generating value by creating new drugs with existing molecules for the treatment of different diseases, changing the chemical formulation or active ingredients in order to reduce side effects and increase drug's efficacy, creating combination drugs, reducing the number of doses in order to increase patient's adherence and finding new delivery methods for certain patients' groups, such as paediatric and elderly patients, who could not take the drug in its original form. (3)

Regardless of the industry, innovation is a complex process with many dimensions. The initial step of the process is usually problem identification followed by idea generation, evaluation, challenges and problem solving, development, first use, commercialisation and diffusion. (4)

In the health care industry in order to initiate the process of innovation, we should begin with an in-depth analysis of the challenges that emerge from the five key stakeholders – patients, physicians, regulatory agents, innovator companies and organisations – with regards to their needs, wants and expectations. From the patients' perspective, reduced waiting time and improved physiological well-being extend life expectancy. Physicians and other caregivers want improved diagnosis and treatment and better clinical outcomes. The regulatory agents target reduced risks, improved patient safety and reduced costs. The innovator companies and organisational expectations are improved outcomes, more effective R&D and profitability. Any attempts at modelling the process of health care innovation must take into account all of the five key stakeholders. (1)

In the past, innovation in the pharmaceutical industry was the result of the findings of basic science translated into clinical compounds, ending up as marketed drugs. This model served as the driver of the R&D and innovation process for many years. The players of this linear model were firms, universities and specialised suppliers. This model is not valid anymore since significant changes have occurred that reshaped the drivers of innovations

and required review of the key players. Rising costs, increased competition, new scientific and technological developments and well-informed patients created a much more challenging environment. (5)

## Challenges

The current situation for the research-based pharmaceutical and biotechnology industry is quite challenging. The political, economic, regulatory and scientific forces have led the companies first to re-evaluate outdated R&D strategies and practices, and, second, to adopt new systems in order to create innovative products more efficiently and in a cost-effective way. Increased market expectations, patent expirations of top-selling drugs, new and stringent regulatory hurdles, loss of public confidence and support, cost and risk inherent in new drug development were the main challenges that forced the industry to reshape its approach. (6)

Despite the fact that the pharmaceutical sector invests \$50 billion annually for research, 'the number of new drugs approved per billion US dollars spent has halved roughly every 9 years since 1950, falling around 80-fold in inflation-adjusted terms'. Pharmaceutical companies have invested enormous amounts in the research of new molecular entities (NME), however, the approval rates from phase I are only 7% for cardiovascular disease, dropping to 4% for Alzheimer's disease.(7) In 2007, 16 NMEs were approved by the FDA, which was the lowest level since 1983, when 14 were approved.(6) The increasing cost of R&D is not indicative only of the quality of research management quality. It also shows the difficulty to address therapeutic areas that have incredibly complex biological mechanisms, which is also depicted in the failure rates. (7)

The current worldwide policies focus on containing health care costs and restrictive price control forcing companies to provide the therapeutic and economic value of their product than simply demonstrating that is safe and effective. In the United Kingdom, for example, the National Institute for Health and Clinical Excellence (NICE), which makes reimbursement recommendations to the National Health Service, recently determined that reimbursement should be restricted or denied for a host of cutting-edge biological products. In United States, third party payers and health plans have become increasingly restrictive on the level of coverage they are providing for new pharmaceutical and biopharmaceutical products. The above-mentioned measure, in addition with current efforts to make standards for the way the comparative effectiveness

research (CER) is performed, suggests that the focus on product value will probably escalate in the coming years. On the other hand, the increased public concern about drug safety has raised the regulatory hurdles for new drug's approval.

Based on a Tufts Center for the Study of Drug Development (CSDD) analysis of NMEs and NBEs recently approved by the FDA, the average time to bring a product from the start of clinical testing to regulatory approval is 7.2 years. In addition to long development times, average clinical success rate is currently 16% for pharmaceutical products. (6) Meanwhile, clinical trials still focus on scientific endpoints, instead of participants' experiences and outcomes with the application of surrogate markers and laboratory tests not explaining what actually happens to patients. (8)

The result of the above-mentioned practices is high overall R&D cost. Based on Tufts CSDD published data, the average capitalised cost to bring a new biopharmaceutical product to market, including the cost of failures, is \$1.24 billion, in 2005 dollars, and \$1.32 billion for traditional pharmaceutical products.

The greatest challenge the industry faces is the length, risk and cost of pharmaceutical and biopharmaceutical development. Even after twenty years of focus on R&D efficiency, the progress the industry has made in shortening time-to-market, optimising clinical success rates and lowering the total cost to bring new products to market is rather small. And for a research-based industry, fewer products reaching the market means less probability to raise revenues in order to sustain growth and support the increased cost of pharmaceutical R&D. (6)

## Current and Future Objectives

There is an emerging need to move from the constraints imposed by property rights to a new era of 'open innovation'. In order to improve research productivity, the pharmaceutical industry can share the vast creative, intellectual and technological resources in order to create from the riches of the genome that are now available and new treatments. Whether by sharing chemical libraries, clinical data or establishing patent pools, coordinated and committed collaboration will lead to innovation that holds the key to discover, develop and deliver medicines to patients. (9)

Disease affects not only the individual but the society in its entirety. The 'patient-centred' approach, with the recognition of the medical needs of the population as the key priority, has led to collaborative initiatives between public and private infrastructures in order to accelerate

the discovery of new drugs and deliver better outcomes. (9) Academia, nonprofit/ for-profit research institutions, government agencies, pharmaceutical industry and disease-oriented groups working together can lower the complexities and expense of R&D while providing access to innovative drugs to patients in a much less time. (8)

From an industry perspective, there are few key points in which pharmaceutical companies need to focus in order to adopt innovative business models and implement novel strategies. First of all, more emphasis has to be given to the 'economic value' of a therapy as a criterion for R&D investment and following commercialisation. Nowadays, payers demand novel therapies that improve overall patient outcomes, which is translated into a cost/benefit trade-off outcome in regards with the total cost of treatment and subsequent disease management. In most countries, the government has set as a prerequisite for pricing and reimbursement approval of a new drug comparative effectiveness studies supported by evidence.

The second and very important is the shift from 'blockbuster drugs' to personalised medicine. This approach is not only adopted by research laboratories in academia but is also supported and funded by many companies in the industry. According to a survey by Tufts Center for Drug Development, in the last 5 years almost 94% of companies increased their investments in personalised medicine by 75%. What is also very important from that study is that 12% to 50% of current clinical pipelines are based on personalised medicine.

Last, investing in new IT technologies will help to drive efficiencies and enable innovation.

The implementation of EMR/EHR among patients and providers aims to improve coordination of care and clinical decision making, reduce medical errors and increase the use of health outcomes in the decision-making process. Furthermore, the secondary use of EMR/EHR data has the potential to augment and improve clinical development, reduce adverse events and develop credible evidence for comparative effectiveness. For instance, the Partnership to Advance Clinical Electronic Research consortium (PACeR) is investigating ways to utilise EMR data to improve patient selection, protocol design and modelling. Other technologies such as mobile and cloud platforms are transforming business processes to achieve cost savings for the system and better health outcomes for patients.

In an industry that is heavily regulated, any change might be viewed with scepticism. With a vision of modernisation and an implementation path involving public-private partnership, the health care environment will move to the right direction. (10)

## The Innovative Medicines Initiative (IMI)

IMI is a public–private partnership between the European Commission and EFPIA, aiming at improving health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need. IMI projects involve the collaboration of public–private consortia. Pharmaceutical companies contribute to IMI projects with in-kind contributions, which are matched by the EC with funding in cash for participating public entities.

The experience gained from ongoing IMI projects provides evidence that the sharing of know-how and data sets among pharmaceutical companies, academic teams and small businesses delivers results that could not have been obtained otherwise. By providing a neutral platform for a healthy dialogue among the various partners, the IMI fosters the emergence of new mind-sets, both in industry and in publicly funded organisations, especially academic institutions. (11)

- **The Innovative Medicines Initiative 1 (IMI1)**

The Innovative Medicines Initiative (IMI) was launched in 2008 by the European Union and the EFPIA, with a total budget of €2 billion to be spent over a 10-year period, in order to promote innovation and investment in the biopharmaceutical sector across Europe for the benefit of all stakeholders. Significant results have already been obtained like the NEWMEDS consortium that has created the largest known database of studies on schizophrenia, gathering information on 20,000 patients or more in more than 25 countries. This consortium, which brings together thirteen pharmaceutical companies, seven academic teams and three SMEs, offers the industry and the academic community unique opportunities to develop tools, methods and models to discover innovative treatments for schizophrenia. There are numerous other examples of consortiums that were created during the IMI project and produced innovative tools or treatments for other therapeutic areas as well. A major mission of the IMI is to train a new generation of scientists who will be fully acquainted with the complexity of pharmaceutical R&D and open to collaboration across conventional boundaries.

- **The Innovative Medicines Initiative 2 (IMI2)**

As the potential of IMI has been realised by public and private partners, the IMI had to re-evaluate its goals and perspectives: from simply targeting to develop tools and methodologies to programmes

that span across the full value chain from R&D to patient access. IMI2 (2014–2024) offers the unique opportunity to facilitate the much-needed partnerships between drug developer, patients, citizens and regulators, HTA agencies and health care providers to inform early research activities, facilitate uptake of innovation into development programmes and clinical practice, and accelerate patient access. By bringing key stakeholders together, IMI2 has the opportunity to revolutionise the current drug discovery and development process and continue to build Europe as a global leader in the delivery of health care solutions for medicines of priority to society.

IMI2 focus on addressing scientific challenges where multi-stakeholder input is essential for success. These efforts can be captured under four major topics:

1. **Target validation and biomarker research** (efficacy and safety): Failure of efficacy in translating pre-clinical models to the clinical setting, combined with the emergence of adverse events not predicted from the pre-clinical models, remain the most frequent cause of failures in the late stages of clinical development. IMI2 will leverage the availability of the complete sequence of the human genome and the growing body of ‘-omic’ data sets and epigenetic markers, the availability of patients’ electronic medical records, next generation genetics for target identification and sophisticated bioinformatics in order to develop the capabilities, biomarkers and tools required to better inform drug and vaccine developers to identify failures earlier in order to significantly improve the overall productivity of R&D.
2. **Adoption of innovative clinical trial paradigms.** In an attempt to decrease clinical development times and cost, a number of innovative adaptive designs have been introduced. Bayesian statistical methods are being used increasingly in clinical research to minimise the number of patients included in a randomised clinical trial (RCT) and decrease the chance of maintaining a patient in an unfavourable treatment arm. Accumulating results can be assessed at any time, including continually during the study, with the possibility of modifying the design of the trial; for example, by slowing (or stopping) or expanding accrual, unbalancing randomisation to favour better performing therapies, dropping or adding treatment arms, and changing the trial population to focus on patient subsets that are responding better to the experimental therapies.

3. **Innovative Medicines.** The ageing population and increased incidence of chronic disease is driving the need for investment in developing new therapeutic strategies that integrate early detection and prevention. In addition, there are a number of diseases, which, although they place enormous burden on the health care systems of today, pharmaceutical companies have largely withdrawn from – either due to high risk of failure or due to the lack of return on investment.
4. **Patient-tailored adherence programs.** The concept of precision medicine is also to create tailored treatment programmes designed to maximise beneficial health outcomes and reduce the incidence of non-adherence with prescribed medicines. To achieve this, it will be essential to better understand pharmacology and perception, individual patient behaviours, societal, lifestyle and environmental factors that influence the engagement of patients with their treatment pathways, an area which to date has been undermined (12)

## MAPPs: a new regulatory paradigm that favours timely access to innovation

Medicine Adaptive Pathways to Patients (MAPPs) build on the stratification breakthroughs of personalised medicine to facilitate new types of clinical trials that adapt to a given patient's response. At their core, MAPPs will have a limited commercial marketing authorisation for a patient group who has access to new therapeutic agents while validating additional clinical endpoints at the same time. This gives MAPPs a theoretical ability to run trials that fulfil both the efficacy requirements for authorisation and the effectiveness needs of national health technology assessments (HTA) simultaneously, providing patients with needed therapies in the most efficient timescale and trial size possible. In order to move science forward and meet the daunting medical challenges for patients, new collaborative approaches to testing the efficacy and effectiveness of new improved medicines such as MAPPs should be embraced by regulators in close partnership with patients, payers and practitioners. Otherwise, the entire health care value chain, and the future health of patients, is put at risk.

One of the earliest examples of an adaptive trial was launched in 2008 by Don Berry, head of Quantitative Sciences at M.D. Anderson Cancer Center in Houston Texas for breast cancer, under the moniker of I-Spy 2. A key to a limited authorisation will be the harnessing of 'real world evidence' to monitor the approved cohort with

new tools and strategies being developed and tested under the Digital Agenda mandate of the European Commission. The regulatory research objectives of MAPPs will be placed into an IMI2 proposal pipeline for validation. MAPPs gain valuable information about multiple endpoints while making a new therapy available to patients in as timely a fashion possible when supported with data for a targeted indication. This approach should also incur fewer adverse events and less toxicity, as the limited initial licence will be focused on those most likely to respond. It can also radically reduce the time to market for new therapies, relieving pressure on the exponentially increasing costs of RCTs.

Further, a key component of MAPPs will be need to monitor in real time the response of patients to new therapies, both for better outcomes, and avoidance of adverse events. The information technology (IT) infrastructure and interoperability to provide the needed evidence base across multiple regional and national health jurisdictions is currently lacking in the EU, but there are programmes running to investigate and support enhanced health informatics and electronic patient records. These will need to be tested, proven and implemented in conjunction with MAPPs platforms under IMI2.

Ultimately, MAPPs supports the patient's need for timely access to effective innovative medicines. It will reduce research barriers and improve efficacy, increasing innovation in the life sciences creating benefits to society. It can improve the efficiency of health care delivery, providing the data required to evaluate new therapies in a more timely fashion while supporting innovation, increasing effectiveness and promoting investment by the European pharmaceutical sector. We are moving into an era where 'getting away' with as little testing as possible is an essential feature of successful innovation – so long as that testing is done in a real context where the results are believable. (7)

## Horizon 2020

Horizon 2020 is the biggest EU Research and Innovation programme ever with the budget of almost €80 billion of funding for the next 7 years (2014–2020). Horizon 2020 is the financial instrument implementing the Innovation Union Europe 2020, a flagship initiative aimed at securing Europe's global competitiveness. Horizon 2020 follows achievements in the previous programme, 7th Framework Program for Research and Technological Development (2007 to 2013). Horizon 2020 differs in the structure from FP7, by coupling research and innovation, aiming to achieve this with its emphasis on excellent

science, industrial leadership and tackling societal challenges. The goal is to ensure that Europe produces world-class science, removes barriers to innovation and makes it easier for the public and private sectors to work together in delivering innovation. (13)

## Benefits of Innovation

### Personalised Medicine

Personalised medicine is the use of each patient's molecular and genetic profile in order to adopt its treatment to its individual characteristics. The innovative part in personalised medicine is the use of advantages in molecular biology and methods by the physician to choose from the therapeutic protocol of a disease that is based on existing therapies the optimum one, matching to patient's profile, minimising side-effects while maximising the outcome, avoiding the previous 'trial-and-error' approach. Personalised medicine has already proven its significant impact on clinical research and patient care and is expected to offer more as technologies improve.

In contrast with gene therapy, personalised medicine is already in clinical practice. One of the earliest and most common examples of personalised medicine is in breast cancer. For patients with breast cancer, expression of protein HER2 is a predictive marker for response to therapy. Overexpression of that protein is linked with patient's tolerance to standard therapy. Based on the molecular profile, Trastuzumab was approved for patients with HER2-positive tumours in 1998. A follow-up study in 2005 showed that, when used with chemotherapy, it reduces recurrence by 52%.

Another example is imatinib mesylate. Approved in 2001, indicated for patients with chronic myelogenous leukaemia (CML) that had an acquired genetic aberration in the tumour cells, known as the Philadelphia chromosome and/or the BCR-ABL gene. This targeted therapy in patients positive for this particular cytogenetic biomarker improved their survival significantly. In an analysis of more than 3,000 patients diagnosed with CML in the Swedish Cancer Registry between 1 January 1973, and 31 December 2008, survival proved to increase significantly after 2001. In particular, 5-year survival rates were 0.21 for the period 1973–1979 compared to 0.80 for the period 2001–2008. But the added value of imatinib mesylate was only realised after its combination with the biomarker that could identify the patients that would benefit from this new therapy. (28)

As expected, precision medicine attracted the centre of attention in the world's health care goals today.

On 21 January 2015, US President Barack Obama called for a Precision Medicine Initiative in which cancer was set as one of its immediate targets. This cancer precision medicine initiative will use all latest advances in biotechnologies, such as next generation sequencing, proteomics, transcriptome, epigenetics, pharmacology and bioinformatics, in order to identify exact causes for cancers and develop personalised therapies for patients. Consequently, this initiative rapidly found takers throughout the world. In March 2015, China announced their Precision Medicine Initiative, in which it plans to invest a total of 60 billion Renminbi in search for prediction of hereditary diseases in newborns, investigations on antibiotics resistance, preventive measures development and personalised cancer therapy. The United Kingdom also announced a 100,000 Genomes Project involving 70,000 participants. (29)

As the ecosystem of stakeholders has recognised the added value and works to advance personalised medicine, collaboration with government regulators and policymakers is necessary to encourage and widespread further the use of these new tools and technologies. The regulatory process must evolve in response to advances that are targeted to smaller patient populations based on genetic profiles, and policies and legislation must be enacted that provide incentives for innovative research and adoption of new technologies. Together, progress in the research, clinical care and policy enabling personalised medicine has great potential to improve the quality of patient care and to help contain health care costs. (14)

### Gene Therapy

With the term 'gene therapy', we describe the genetic modification of cells by providing them the functional copy of the deficient gene that is responsible for a particular disease. In the beginning, gene therapy's focused area was inherited genetic diseases. However, gene therapy can also be applied in cancers and, in general, for the treatment of non-hereditary diseases. About two-thirds of the total clinical trials that are being carried out worldwide concern different types of cancer. (15)

Most scientists believe that gene therapy is the most exciting and promising application of DNA science, but still an experimental discipline. In fact, they consider it to be the cure of every genetic disease in 20 years' time. Taking advantage of the completion of genome mapping and the knowledge of gene function and their implication in disease, gene therapy provides a permanent cure of the disease not accessible by any other current alternatives. (16)

In fact, the clinical trials that have been carried out have already proven its therapeutic value in various diseases, such as Parkinson's disease, Alzheimer's, cystic fibrosis, diabetic neuropathy, metastatic melanoma and others. (17) Should the disadvantages of gene therapy, such as the short-term nature and the immune response, as well as the ethical issues get over, gene therapy has the potential to overwrite most of the current therapeutic approaches.

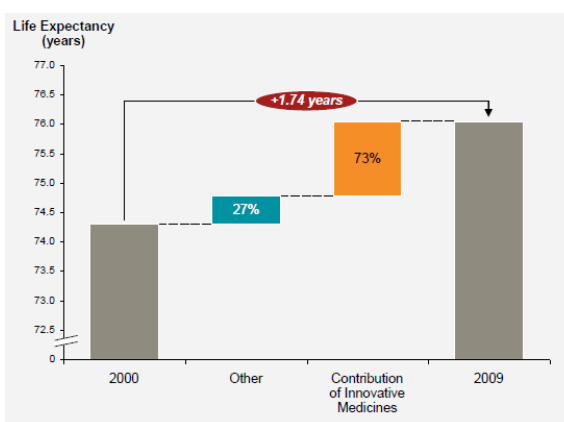
## Increased spending on cancer care leads to decrease in Cancer Mortality

A recent study that was performed in sixteen countries between 1995 and 2007 analysed trends in cancer spending and mortality rates. The results showed that cancer mortality was reduced by 17 percent in countries that had the highest increase in cancer care spending during that period. The mortality benefit was only 8 percent in countries with the lowest spending increase. High-spending countries also earned a higher rate of return for every additional dollar spent on cancer care. For every additional \$1,000 spent, the average country had 0.39 fewer cancer deaths per 100,000 whereas that number jumped to 1.65 fewer deaths for high-spending countries. A potential reason for this difference is that high-spending countries may use health care resources more efficiently and may provide more treatment options for each condition. In addition, as developers of new technologies, these countries are also likely to adopt them quickly. Low-spending countries, by contrast, tend to delay access to new treatment options until they have first been proven elsewhere.

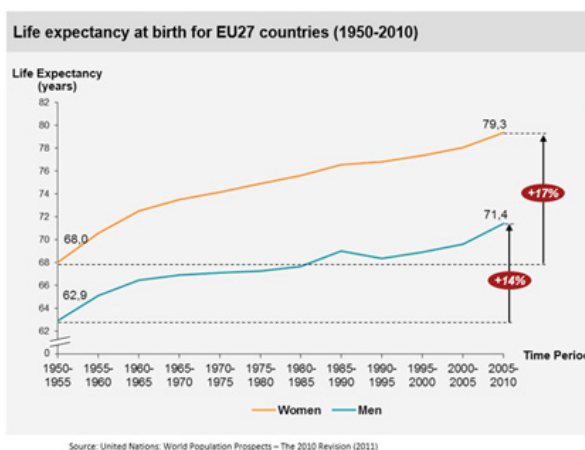
As the author argues, denying or delaying the introduction of new technologies doesn't have any real value to a society, in the long run since system will always improve. (18)

## Contribution of innovative medicines to increase in life expectancy

In a study published in 2013 by Frank Lichtenberg (19), the impact of pharmaceutical innovation, as measured by the vintage (world launch year) of prescription drugs used, was evaluated on longevity using longitudinal, country-level data on 30 developing and high-income countries during the period 2000–2009. As shown in Figures 1–3, from 2000 to 2009, an improvement in life expectancy that was observed was mainly attributed to innovative medicines usage. (19)



**Figure 1.** Innovative medicines are estimated to have contributed to 73% of this improvement once other factors are taken into account (e.g. income, education, immunisation, reduction in risk factors, health system access). Lichtenberg, F: *Pharmaceutical innovation and longevity growth in 30 developing OECD and high-income countries, 2000 - 2009* (2012) (19).

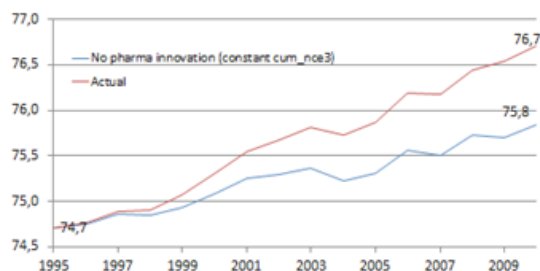


**Figure 2.** During the last 60 years, life expectancies have improved substantially across Europe in both genders (Lichtenberg, F: *Pharmaceutical innovation and longevity growth in 30 developing OECD and high-income countries, 2000 - 2009* (2012)).

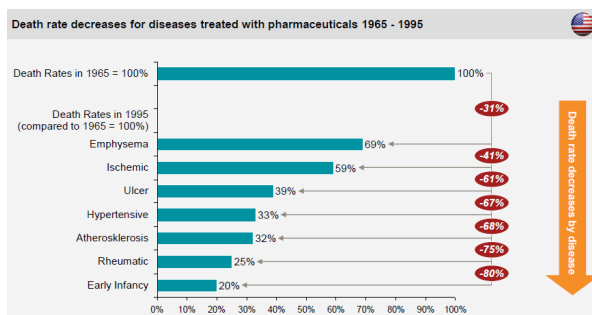
## Innovation in medicine has made major contribution to reducing mortality rates in many priority conditions

As shown in Figs. 4 and 5, the contribution of innovative medicines in increasing life expectancy and decreasing mortality rates has been evaluated in United States of America as well. The results were in line with the results from the studies performed in Europe proving the major contribution of innovation in life expectancy. (20)

### Mean age at death, Greece, 1995-2010



**Figure 3.** During the last 60 years, longevity has increased 2.00 years in Greece. The estimates indicate that 44% of this increase was due to the introduction of new drugs during the period 1992–2007. (Lichtenberg, F: *Pharmaceutical innovation and longevity growth in 30 developing OECD and high-income countries, 2000 - 2009* (2012)).



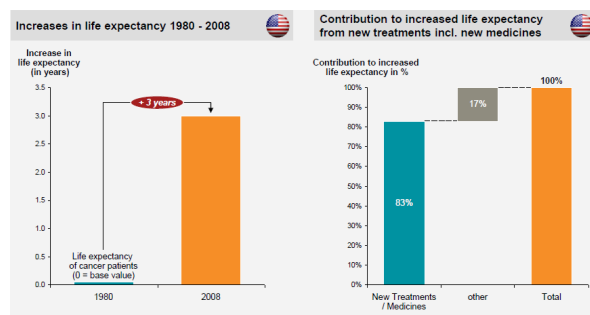
**Figure 4.** Death rate decreases for disease treated with pharmaceuticals 1965–1995. (PhRMA, 2012).

## The industry continues to invest in innovating new oral forms in line with patient preference

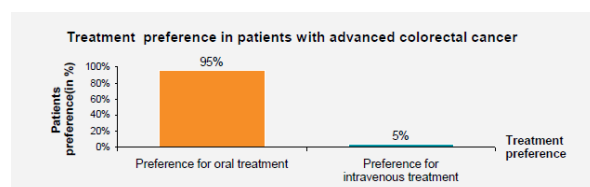
In terms of adherence, oral drugs have a potential advantage over injected therapies. Generally, they are perceived to be better tolerated, physically and psychologically. (Fig. 6) (21)

## Biomarker-driven phase II trials slowly replace large randomised phase III trials

The traditional approach to the development of anticancer drugs, with new therapies screened in phase II trials and subsequently tested in large phase III trials when promising activity, has shown to be time consuming. (22) Modern innovations in clinical trial



**Figure 5.** In areas like cancer, medicines innovation continues to play a key role in increasing life expectancy (PhRMA, 2012).



**Figure 6.** Twelves, C., et al., A randomised cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer.

design have led to the availability of new approaches referred to as adaptive seamless designs (ASDs). (23) Combining phase II and III trials together in a phase II/III design has gained focus since it is more efficient in streamlining the timeline and also allows the data from phase II patients to be used in the analysis of phase III, reducing the total number of patients. (22)

ASDs use primary endpoints, such as biomarkers or survival analysis, as treatment selection for phase III. The most common trial designs with integral biomarkers are:

- Randomised block designs, where the biomarker is used to define a stratification factor for randomisation
- Marker-enrichment designs, the biomarker is used to select the sub-population for investigation; it can be a predictive marker for patient response to treatment, or prognostic marker for the identification of high-risk patients in which a new therapeutic may be of clinical benefit
- Marker-directed designs, where treatment assignment is determined by the integral biomarker; for example, assigning marker positive patients to the hypothesised optimal treatment (predictive marker), or to the more aggressive treatment (prognostic marker). (24)

In a study published in 2013, the trials performed for lung cancer presented at the American Society of Clinical Oncology (ASCO) Annual Meeting were summarised. The aim of the study was to demonstrate that clinical trials using histology or molecular biomarker selection criteria are more likely to have statistically significant improvements in survival outcomes. Indeed, many of the trials that selected for molecular biomarkers, such as EGFR mutations and ALK rearrangements, have proven a significant benefit in PFS for patients receiving appropriate targeted therapy compared with cytotoxic chemotherapy. Although these trials failed to show an OS benefit, other data from the Lung Cancer Mutation Consortium had validated this notion by reporting an improvement in OS for patients treated with targeted agents based on molecular biomarkers compared with those with molecular biomarkers treated with conventional chemotherapy. These data support the use of biomarker selection criteria in clinical trial design as a strategy to increase the possibility of positive clinical trial outcomes. As more trials adopt these strategies, specific treatments that are more beneficial for patients with select tumour characteristics can be identified, and eventually different treatments from various trials can be available to deliver personalised medicine for patients. (25)

Additionally, biomarkers have accelerated the development of treatments in some types of cancer, HIV infection, atherosclerosis and multiple sclerosis, whereas cancer-specific fusion transcripts or mutations, viral load, plasma levels of low-density lipoprotein cholesterol and brain MRI (magnetic resonance imaging) white matter lesion burden, respectively, have been used to evaluate the benefit of the candidate drug. Furthermore, such studies may help to bridge the gap between animal studies that are poor at predicting treatment success in humans and large clinical trials. (26)

In conclusion, adaptive trial designs are generally more efficient as they combine two studies into a single study, utilise data collected from both stages in the maximum level, reduce significantly the lead time between studies, shorten the development time of a new drug, (27) thus maximising patients' benefit since it provides access to new therapies faster and personalized based on patients' molecular profile.

## Conclusions

Pharmaceutical companies encounter unprecedented challenges in their effort to bring innovative new therapies to market. Rapidly growing R&D costs, increasing competitive pressures, new regulatory hurdles and a

highly volatile public and political climate represent significant threats to the research-based industry.

Innovation is the only road to reshape health care environment, providing patients' with the best clinical outcome while taking advantage of the available resources and technologies in the optimum level for the payers and the industry. Advances such as the molecular understanding of the disease and the sequential successful development of targeted therapies as a result of personalised medicine, have changed clinical practice, while improving quality of life and reducing mortality for patients. The need for an innovative clinical trial culture that matches the trial to the patient, rather than finding the patient for the trial is becoming a reality, but still there is room for improvement. Clinical trials and clinical research should be more cooperative, bridging the academia–industry intersection, delivering the maximum benefit to the patients in an affordable health care system. The new partnership models that have begun between public and private sector with already delivered results should be enhanced, leveraging international collaboration.

The move to a patient-centred approach, with patients' engagement in clinical research and their involvement in the decision-making process, is one more example of innovative approach. As technology advances, the move to the future setting scene for the virtual clinical trial, where the deployment of computational models to predict patient responses to drugs in silico, with applications in personalised medicine and drug development and discovery will take place, further decreasing of costs and faster access to new therapies for patients will be feasible.

The establishment of the evidence-based era has also begun. As the evidence base will increasingly involve the generation and analysis of real-life data, the dialogue between stakeholders should be initiated early to ensure that innovation and better clinical outcome is rewarded, while therapies with a limited potential fail at an earlier stage, limiting costs and removing patients from clinical trials with little or no clinical benefit. Developing a closer and earlier dialogue between researchers, industry, regulators and payers in this rapidly evolving landscape will inform a more progressive approach that balances the patients' rights with the need to improve the health and wealth of citizens and societies. Regulatory frameworks should keep pace with the evolving health care landscape and not hamper the successful integration of innovation into health care systems. The era of the innovative, research-based delivered therapies that improves outcomes but also ensures timely access for patients has begun. We should continue the endeavour to improve current

situation based on tools and methodologies we already have but we must not forget to follow up as science and technology are limitless and their advances will always have the potential to deliver us in a promising future.

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