CHAPTER 29

Will You Move The Needle of Medicine?

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PERSPECTIVES

We certainly are living in a most scientifically interesting time. Data volume in science is, at least, doubling each year, and the knowledge derived is also growing exponentially as the reader will have gathered from the evidence in this book (Marx, 2013). We have certainly come a long way from those days of Voltaire, when he said that '*L'art de la médecine consiste à distraire le malade pendant que la nature le guérit*'[1]. Francis Bacon was a little more perceptive when he said, in the 17th Century that '*He that will not apply new remedies must expect new evils, for time is the greatest innovator*'. Indeed, as we have seen in recent history from HIV's arrival and that of Hepatitis C in the 1980s, to the outbreak of Ebola in recent years, viruses, bacteria, cancer cells and cancer stem cells all show an amazing ability to mutate, which leads to new diseases and the evolution of many known diseases, which Society has to contend with as challenges to 'Health'. Abraham Maslow and others have long recognised that good health features high in our hierarchy of needs (Maslow, 1943). Once a person has food in the stomach and a 'roof' over the head, the next priority is 'health'. Approaching 8 billion people now live on our planet Earth, and while we still have abject poverty in many parts of our world, we have also seen an amazing rise in living standards in many areas leading to more and more people reaching that need for good health (Easterlin, 2000). Following the '*romantic*' era where medicines were almost exclusively derived from plant extracts (Anonymous, 1440; Lemery, 1714), the rise of antibiotics was the first '*modern*' revolution in healthcare, with the '*postmodern*' revolution being that enabled by the technology of 'gene splicing' that led to mAbs, and now nucleic acids therapeutics, gene-based therapies and engineered cell-based therapies, with the '*hypermodern*' revolution being that of precision and personalised medicine (Aminov, 2010; Brown and Wright, 2016; Collins and Varmus, 2015; Fleming, 1944; Liu, 2014; Wade, 1980); these transitions are at the heart of pharmaceutical business strategies (Kasparov, 2005; Pisano, 2015). Society around the world has already made major decisions that already affect our demand for healthcare. Notably, more than half the world's population has moved into an urban setting following the rise of industrialisation of many economies. With this move, we have had many positive effects such as availability

[1] 'The art of medicine consists of amusing the patient, while nature cures the disease'.

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of clean water systems and sewage infrastructure contributing to our increasing life expectancy (Easterlin, 2000; Riley, 2001). On the other hand pollution in our cities has resulted in challenges to our immune system as evidenced in the increasing prevalence of asthma (Anderson et al., 2013). Societal pressures have also brought an increasing prevalence of mental illnesses such as schizophrenia (Link and Phelan, 1995; Selten et al., 2013). Living longer, but in many instances with increasing morbidity, has resulted in greater demand in our societies; however, in many parts of the world, we are not fully recognising these forces and the tough choices Society has to make. This raises the thought of 'What healthcare goals should we have for Society?'. At the founding of the World Health Organization (WHO) in 1948, this was defined as follows. The goal should be 'a state of complete physical and societal wellbeing and not merely the absence of disease or infirmity' (Huber et al., 2011; Manderson and Nile, 1958). Contrast this definition, if you will, with one proposed in 2011 in the British Medical Journal where the health goal was defined as 'the ability to adapt and self manage in the face of social, physical and emotional challenges' (Huber et al., 2011). This latter definition would mean that each of us is 'on our own' to find healthcare solutions. This concept is embodied already in increased input, and impact from patient advocacy groups and patient engagement, notably, enabled also by personalised medicine technologies that are becoming more widespread (Anderson and McCleary, 2015; Aspinall and Hamermesh, 2007; Buttle and Boldrini, 2001; Domecq et al., 2014; Hamburg and Collins, 2010; Schork, 2015). From a societal point of view the writer favours the WHO definition as the aspirational goal for Society to strive towards and for life science researchers or drug developers, in both academia and public service as well as in industry, to make significant contribution towards. To harness the exponential rise in our knowledge towards that goal, our common critical challenge is to move the needle of medicine sufficiently that Society appreciates the progress thus achieved and is prepared to pay for.

With this in mind, let us consider 'Innovation'. Over this writer's long career in the life sciences sector, I have observed that much innovation happens at interfaces rather than in intellectual silos. Multidisciplinary groups, whether gathered around the water cooler or on sites that are not too big for this to happen, and with people who have open minds to make the chance observation, and then the tenacity to pursue, and make the difference. So, as our knowledge grows exponentially, we think of the S-curve of innovation of breakthroughs from proteins drugs to monoclonal antibodies, from stem cells, gene therapy, to engineered living drugs comprising CAR-T cells and CRISPR-cas9 engineered cell-based therapies. The journey for these achievements from discovery to 'moving the needle' in clinical practice can take decades, from the 'Eureka' moment through the valley of despair to ultimately reach an understanding of the role of the new innovation in medicine. Today, some phases are moving faster scientifically whereas others are having encouragement from national regulatory authorities. Examples here are from Japan with a new faster approach for regenerative medicine and cell-based products, to the Food and

Drug Administration of the United States passing the 21st Century Cures Act, breakthrough designations and Orphan Act, all facilitating faster possibilities for approvals (Morrison, 2018; Sipp and Okano, 2018). As researchers respond to this new environment, remember again the key question, 'Does the intervention move the needle sufficiently that Society appreciates and is prepared to pay for?' So, remember to do the experiments that not only establish the Proof-of-Principle/-Concept/-Activity/-Safety, but also that you consider the Proof-of-Relevance to medicine and Society (cf. Fig.29.1). This Proof-of-Relevance needs to be measured not only against today's standard of care but also assessing the competitive landscape of both direct competitors in the same space,

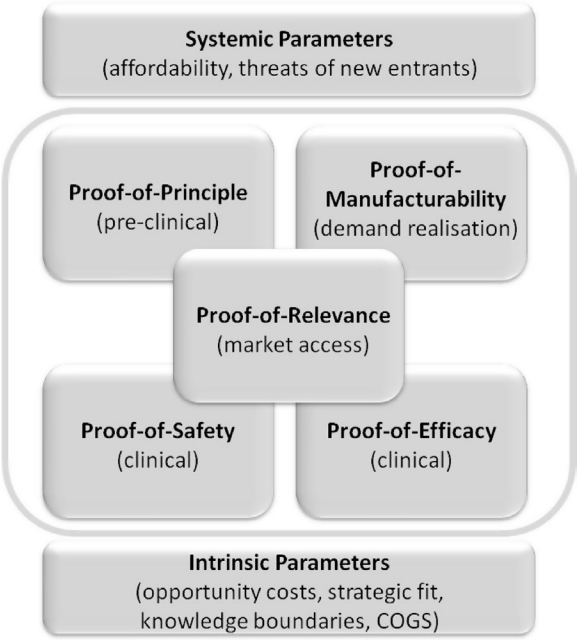

Figure 29.1 ***Strategic checklist for new pharmaceuticals.*** The development of a novel pharmaceutical modality is a critical decision and particularly for paradigm-changing products. Intrinsic and systemic parameters are of major importance. Parameters that are intrinsic to a particular developer comprise opportunity costs, strategic fit, cost of goods, and internal knowledge boundaries. Systemic parameters include not only the threats of new entrants deploying disruptive technology platforms as well as that of competitors in the same arena but also affordability by both payers and patients. Milestones in product development include achieving a preclinical proof-of-principle, as well as establishing in the clinic appropriate confidence in safety and confidence in efficacy, in addition to a robust industrial-scale manufacturing process. Establishing the relevance of the new products to Society's needs underpins the ultimate success of any drug development process. This is particularly true when it comes to advanced therapies that, given their costs of development and production for the foreseeable future as well as the longer term benefits that these products are designed to provide, these disease-modifying or even curative therapies will need to be commercialised at a significantly higher price compared with conventional therapeutics.

as well as looking forward at other disruptional technologies that could totally change the outcomes for patients. The portfolio strategic checklist thus defined is patient- and payer-centric; it adopts a major trend of the current evolution of the pharmaceutical business. Notably, this concept expands that of 'customer value', which already had fundamental applications in numerous other industries (Smith and Colgate, 2007; Woodruff, 1997). As suggested by Michael Porter, in healthcare, '*measuring value should encompass all services or activities that jointly determine success in meeting a set of patient needs. These needs are determined by the patient's medical condition, defined as an interrelated set of medical circumstances that are best addressed in an integrated way. The definition* of a medical condition includes the most common associated conditions — meaning that care for diabetes, for example, must integrate care for conditions *such as hypertension, renal disease, retinal disease, and vascular disease and that value should be measured for everything included in that care*' (Porter, 2010).

What is more, at a high level, we will also see fundamental changes that will dramatically impact the practice of healthcare such as:

- Enabled by dramatic decreases in cost and increases in sequencing throughput (Shendure et al., 2017), a time will come when each newborn child can have a whole genomic sequence made at birth to enable people to better manage genetic diseases and lifestyle choices to enhance wellness.
- Longitudinal health records will enable the measurement of real-world benefits of clinical outcome/safety/treatment changes. Virtual trials will be possible with control groups matched through artificial intelligence rather than prospectively selected to take part in a study. This longitudinal data can also be used to assess real-world costs and health economics. This systems biology revolution is already exemplified by the 'virtual patient' concept of the early 2000s (Kohl and Noble, 2009; Michelson, 2006).
- As biology continues to map patterns of genes and markers, a new taxonomy of disease will emerge in many areas (Barturen et al., 2018; Hofmann-Apitius et al., 2015).
- Given the increasing demand for healthcare, Society will not be able to pay for 100% of costs. Each of us will have to contribute more through insurance, taxes, co-pays, etc.

A more patient- and payer-centric approach is increasingly necessary as science and technology have progressed such that patients take more ownership of their health. Nowadays, individuals are better connected than ever through the Internet with the immediate result that we will have the possibility for a greater say in our healthcare. Reflect that today in the United States more than one-third of visits to primary care physicians start with a reference to the Internet. Equally interesting is the fact unearthed by market research that over 40% of US patients cross-check online after their visits to the doctor. Even if your new intervention is available tomorrow, the 'payer' will look more and more closely at the health economics available, as costs related to the treatment of chronic diseases associated with ageing grow (Goldman et al., 2005). This will be in a spectrum from the very arithmetic approach as in the United Kingdom, Ontario,

Australia or New Zealand, through to those countries with a more societal view or with a Legal Rights-driven set of decisions such as the United States, France, Sweden, etc. So, again, as you formulate development plans for your new approach, build a clear case for your intervention both medically and economically for tomorrow's world.

To be clear, the writer is not advocating a cost neutrality within healthcare for new interventions, but rather one that builds clear advocacy on what you are going to provide and what you will be asking of Society during your products' periods of exclusivity. In conclusion, reflect on how your new approach can positively move the needle of medicine through strong innovation, data driven to make such advancement in a defined group of patients such that you can look Society in the eye and ask for a price that not only passes the 'red face test' with Society but also gives an economic return to the shareholders who took the risk with you. The chapters in this book show that significant progress is really happening on many fronts.

Every success in all the endeavours represented here and by the readers in their drive to move the needle!!

The author William (Bill) Burns is today the Chairman of Molecular Partners and Vestergaard in Switzerland and is Vice Chairman of Mesoblast in Australia. He also serves as a Governor to the Wellcome Trust and the Institute of Cancer Research. He was formerly the CEO of the Pharmaceutical Division of Roche and held the Board memberships at Roche, Genentech, Chugai and Shire.

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