Chapter 19
Challenges to Nanomedicine

Richard Moore

19.1 Introduction

The recent past has seen a period of considerable financial upheaval and constraint that has affected healthcare and healthcare provision like many other sectors. There is an increasing pressure on those bringing forward new medical technologies to ensure that they are capable of outperforming existing, established technologies, that they have a high benefit-to-risk ratio and that they are affordable or can otherwise lead to cost-savings in healthcare systems where resource availability is a constant concern.

While economic factors are particularly sensitive in the current financial climate, there are a number of other important hurdles to be negotiated in bringing any new medical technology to the clinic. These include

- taking account of demographic trends and associated changes in healthcare priorities
- addressing and minimising risks
- understanding which regulatory system(s) apply and ensuring product compliance
- understanding and negotiating reimbursement systems
- preparing for healthcare technology assessment
- considering the impact that emerging technologies may have on established medical practice
- ensuring that there is professional uptake of new technologies and addressing training issues that may arise
- addressing public understanding and perception issues
- in some cases, addressing new ethical challenges that the technology may bring

R. Moore (✉)
Biomimesis, Melton Mowbray, LE13 OUH, UK
e-mail: richard@biomimesis.net

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While some of these topics, such as risk and ethical issues, are explored in greater depth in other chapters, they are reviewed and discussed in the following sections in order to provide a broad overview of some of the important challenges and milestones towards successful commercialization and utilization of medical products based on nanotechnologies.

19.2 The Rising Costs of Healthcare

It is estimated that, in all countries, both health and long-term care will drive up public spending. In the recent OECD Economic Report No. 6, De la Maisonneuve and Oliveira Martins (2013) project that, for OECD countries, average public healthcare expenditure will increase from 5.5 % of GDP in 2010 to 8 % of GDP in 2060; whereas public long-term care expenditure will increase from 0.8 % to 1.6 % of GDP in 2060 [1]. The report projects that healthcare spending will be pushed up mostly by the combined effect of technology, relative prices, and factors such as institutions and policies, while pressures on long-term care costs will originate mostly from weaker productivity gains than in the economy as a whole.

Given the competing pressures from other social spending programmes, the report concludes that projected trends in public health and long-term care spending are likely to be a major source of concern for most governments.

A key challenge for nanomedicine will be to demonstrate that it can contribute towards containing these rising costs. Given that the implementation of technology is frequently cited as contributing to rising healthcare costs this may at first seem paradoxical. However, a major component of the cost of healthcare is hospitalization and reducing the length of stay (LoS) in hospital is a major objective for new treatments and for healthcare planners. Nanomedicine may be able to contribute to reducing the duration of in-patient stays, or to eliminating them altogether, in various ways including:

- facilitating earlier, faster or more accurate diagnosis thereby potentially reducing the length of treatment required;
- contributing to the efficacy of treatment and improving the prognosis for the patient;
- facilitating treatment at home, at the GP's surgery or as an outpatient;
- improving the performance of individual drugs and medical devices;
- contributing to personalized medicine, e.g. by selecting and tailoring treatment to suit the individual patient and their condition.

Robinson and Smith [2] suggest, for example, that there are numerous examples of new products and processes in healthcare that reduce rather than increase the rate of spending growth and that, without these, total costs would be increasing even more rapidly than they are. These include:

- innovative new drugs, tests, devices, and other products (as distinct from services) that are cheaper to manufacture or use than those they replace;

– changes in processes that allow less highly trained but sufficiently competent workers to substitute for more highly trained and expensive staff thereby releasing them for more complex and demanding procedures. Examples could include substituting physician generalists for specialists, nurse practitioners and pharmacists for physicians, non-licensed staff for nurses, and family members and patients themselves for paid staff of any kind.
– sites of care that are less elaborate but which are adequate for the tasks under consideration, including the home itself as an effective site for care in the area of chronic illness.

They further suggest that synergies between changes in one dimension of care and changes in the others may be the most disruptive in terms of channelling patients in new directions and forcing major but desirable changes on both manufacturers and medical practitioners – more so than individual changes in products, personnel, or facilities.

Citing experience in other sectors they suggest that cost-reducing innovations are attributable to both new technology, and to new types of business model that are simpler and cheaper than those they replace, resulting in an expansion of the market due to the increased affordability of these services.

Krishna Kumar (2011), with reference to new medical technologies, makes the point that much of the effort of companies relates to providing additional features to score over their competitors' products but that matter very little in day-to-day decisions, while there is very little focus on making technology widely accessible and inexpensive [3].

Health technology assessment and reimbursement schemes, which are discussed later in this chapter, also increasingly focus on cost-containment and value-for-money. Therefore it is important that nanomedicine is able to demonstrate a contribution towards cost-containment within healthcare systems through diagnosing disease at an earlier and more treatable stage, providing more effective treatments, reducing the costs of or extending the life of products, facilitating efficiencies in the delivery of healthcare and the use of professional resources, shortening hospital stays or improving recovery times, or enabling treatment or care to be carried out in less expensive settings. In some cases, cost savings may be realized in the longer term or in parts of the healthcare system other than that where the technology is deployed, necessitating the development of a strong evidence-based case that explains the overall benefits and savings to the system.

A further factor that further exacerbates cost considerations is the demographic shift to an ageing population coupled with a reduction in the proportion of those actively contributing financially to healthcare systems.

19.3 The Demographic Shift Towards an Ageing Population

The European Commission's 2009 Ageing Report [4] estimates that, between now and 2060 within the European Union, the population will shift from a ratio of four people aged between 15 and 64 for each person aged over 65, to a ratio of only two to one.

The largest change is expected to occur between 2015 and 2035 when the current baby-boomer generation will be entering retirement. Between 2010 and 2030, the number of Europeans aged over 65 is expected to rise by nearly 40 % and, by the mid-2030s, the number of people aged 85 and over is projected to double in most European countries. Furthermore, it is estimated that around 50 % of babies born today are likely to live to 100 due to improvements in healthcare and living standards.

These demographic changes are likely to have a dramatic effect on society and to lead to new clinical challenges in relation to a wide range of health conditions associated with the elderly such as cardiovascular diseases, cancers, arthritis, osteoporosis and other orthopaedic conditions, dementias and other neurodegenerative diseases, hearing and balance disorders, and some forms of blindness.

According to the 2012 World Alzheimer Report [5] the costs associated with dementia alone were estimated to be around 1 % of the world's gross domestic product at around $604bn (€421bn) and it is likely that these costs will increase in proportion to the number of people with dementia. The report goes on to suggest that dementia, which comprises a range of neurodegenerative disorders of which Alzheimer's Disease accounts around two-thirds, poses the most significant health and social crisis of the century as its global financial burden continues to escalate, with the number of people with dementia expected to double by 2030, and more than triple by 2050. Around 682 million people will live with dementia in the next 40 years, significantly more than the population of the whole of North America (542 million) and nearly as much as the whole of Europe (738 million).

According to OECD Economic Policy Paper No. 6 [1], in 2010, 60 % of global healthcare expenditures were directed towards people below 65 years old. In 2060, roughly the same percentage of expenditures will be directed to people aged above 65, reflecting an increase from 15 % to 30 % of their share in the total population.

As the proportion of the population at retirement age and beyond increases, the proportion in work is simultaneously decreasing, reducing the tax and national insurance base that supports healthcare services and further compounding the problem of supporting the increasing costs of treating and caring for the elderly. It is also important to note that, as people live longer, they have an increasing and justifiable expectation also to be able to maintain their dignity, independence and quality of life.

Will nanomedicine be able, therefore, to play a role where clinical and care needs are increasing due to this demographic shift and whilst health and care systems are under enormous pressure and costs are increasingly constrained? The following paragraphs provide some examples of research that has been funded by the European Commission and which is aimed at using nanotechnology, sometimes coupled with other enabling technologies, to address the health needs of an ageing population.

The European FP7 project NAD (*N*anoparticles for Therapy and Diagnosis of *A*lzheimer's *D*isease), which commenced in 2008 and conclude in August 2013 is currently evaluating dendrimer nanocomposites for imaging and therapy, nanoliposomes for therapeutic agent delivery and other functionalized nanoparticles for applications in Alzheimer's disease [6].

The FP7 project Development of Novel *Nano*technology Based *Dia*gnostic Systems for *R*heumatoid *A*rthritis and Osteoarthritis (NanoDiaRA), which commenced in 2010 and was due to conclude in January 2014, is developing nanoparticle-based imaging and blood and urine-based diagnostic tools, and biomarkers, for the early detection of osteo- and rheumatoid arthritis. The research may also offer insights into the development of controlled nanoscale drug release and will consider the social, ethical and legal aspects of applying nanotechnology for medical purposes [7].

The FP6 integrated project Lidwine, which concluded its work in August 2010, developed novel approaches, including nanotechnology-treated textiles, for treating decubitus (pressure) ulcers, a painful and serious and, in terms of treatment, very common and expensive condition affecting many elderly bed- or chair-bound patients [8].

Moore (2011) reports other examples of nanotechnology research geared towards conditions affecting the elderly including the development of multifunctional nanoparticles capable of delivering controlled-release therapeutic agents to the inner ear for the treatment of age-related hearing loss and balance problems, and the use of nanotechnology in novel devices such as retinal implants for potential use in serious eye conditions such as macular degeneration [9].

Nanotechnology may also play a role in promoting the efficiency of care of the elderly through networked monitoring and telecare solutions which can be often be interfaced with novel biosensors incorporating micro- and nanotechnology. A variety of sensors can be embedded in the home, e.g. to monitor energy usage, movement or falls, or can be worn by the elderly person to monitor their physiological condition and provide a continuous feedback regarding their well-being or state of health to a remote monitoring station. Such networked systems can be used to alert health services or carers to react where there is an urgent or identified need, thereby allowing limited resources to be targeted more effectively as well as contributing to the independence of the patient.

Rather than being seen merely as an added cost, nanotechnologies should perhaps instead be viewed as a means of enabling novel healthcare and social care solutions and reducing the burden of long-term and expensive treatment of chronic conditions associated with ageing, as well as contributing to the dignity and independence of elderly persons.

19.4 Disruptive Innovation?

Clayton Christiansen (1997) defined several distinct types of innovation as follows:

Sustaining innovation: an innovation that does not affect existing markets.

Evolutionary innovation: an innovation that improves a product in an existing market in ways that customers are expecting.

Revolutionary (radical) innovation: an innovation that is unexpected, but which does not affect existing markets.

Disruptive innovation: an innovation that creates a new market by applying a different set of values, and which ultimately (and unexpectedly) overtakes an existing market [10].

Nanotechnology has the potential to impact medical products and processes at each of these levels. In many cases, the effects will be incremental such as improving the coating on an orthopaedic implant to improve its performance or lifetime or reformulating the delivery system of a drug to provide gradual release of that drug over an extended period.

The use of nanotechnology in new generations of devices such as retinal implants [11] could be considered an example of a revolutionary innovation in that it might have the potential to address currently unmet clinical needs such providing at least a limited level of vision for patients with macular degeneration or retinitis pigmentosa.

However, nanomedicine also has the potential for disruptive innovation. One example is its potential major contribution to the emerging field of regenerative medicine, for example the implantation of a nanostructured material into the body that can stimulate the body into self-repair producing new tissue such as in the regeneration of a damaged peripheral nerve [12] or the production of autologous bone that can be used elsewhere in the body for reconstructive surgery [13]. This type of emerging application may help shape a new future paradigm of medical treatment that could replace conventional treatments and for which major changes in procedures and training could be envisioned. Likewise the coupling of diagnostic and "-omics" tests (genomic, proteomic, metabolomic) with therapies (a concept sometimes referred to as *theranostics* [14–17] could herald a new, highly personalized form of medicine where, for example, the selection of drugs is matched to the individual patient and their condition, potentially reducing the considerable costs of prescribing drugs to patients for whom they have limited efficacy.

Whether the innovation brought about by nanomedicine is incremental, revolutionary or disruptive, there remains the potential for better treatments and lower costs but it is nevertheless important to consider the potential impacts on medical practice and procedures. Furthermore, while a progression towards a more personalized form of medicine may be strongly welcomed by both patients and medical professionals, it may not necessarily match the current business models of the major pharmaceutical and medical technology companies.

19.5 Risks and Regulatory Compliance

Protecting patients from risk is a primary objective of all medical product regulations but how this is actually achieved can vary widely in practice. In Europe, the regulation of the placing on the market of medical technologies is addressed

primarily at the European level. In the US, the Food and Drug Administration (FDA) is primarily responsible. In nearly all countries around the world there are responsible national agencies or government departments.

Long-established product legislation was often drafted in a quite prescriptive style with a form of wording such as "you must not do this", "you shall do that and in this specific way". Many so-called "old approach" European Directives were drafted in this technical style and, as such, were not always adapted very well to areas of rapid innovation as the detailed requirements contained within the legal texts themselves could not always be changed quickly as new technological developments emerged. As this was recognized, newer types of product legislation, such as European "new approach" Directives, were developed which tended to be based around broad safety- and performance-based "essential requirements" rather than detailed prescriptive text, with the technical aspects being addressed in accompanying "harmonized" European standards drafted to support the broad essential requirements of the Directives. Such standards are, in theory, easier to revise if required although this can still be a lengthy process.

The approach taken by the various international agencies responsible for drug and device regulation varies. In the United States, the Food and Drug Administration (FDA) is responsible for determining the *primary mode of action* of the product and this decision will determine the regulatory framework for the product, i.e. a drug, medical device or biological product. The product regulatory application is thereafter managed by the appropriate FDA Center (Center for Drug Evaluation and Research – CDER; Center for Devices and Radiological Health – CDRH; Center for Biologics Evaluation and Research – CBER) with consultations from the other Centers.

In Europe, the *primary mode of action* of the product also determines the regulatory path(s) that will apply. Because European Directives are transposed into national legislation, national agencies and government departments have a responsibility for compliance within their jurisdiction.

The differences between what constitutes a medicinal product and what constitutes a medical device are similar in the US and Europe. In the US, products that have a primarily chemical/metabolic mode of action within the body are defined as drugs and, in Europe, products that have pharmacological, immunological or metabolic primary mode of action are defined as drugs and fall under the Medicinal Products Directive (2001/83/EC) or its related sister Directives or Regulations such as the Advanced Therapy Medicinal Products Regulation (Regulation EC No. 1394/2007). Similarly, in both regions, products that achieve their primary mode of action through physical or mechanical means are defined as medical devices and fall under their own regulatory pathways (the Medical Device Directives in the case of Europe). The European definition of a medical device (Article 1.2(a) of Directive 93/42/EEC) is as follows:

> *… any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories… intended by its manufacturer to be used specifically for……*
>
> – *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
> – *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*

- *investigation, replacement or modification of the anatomy or of a physiological process,*
- *control of conception,*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. [18]

The FDA predicts that many nanotechnology-based products will span the regulatory boundaries between pharmaceuticals, medical devices and biologicals. It has stated [19] that technical assessments will be product-specific, taking into account the effects of nanomaterials in the particular biological and mechanical context of each product and its intended use, and that the particular policies for each product area, both substantive and procedural, will vary according to the statutory authorities. It also advises manufacturers to consult with the FDA early in their development process to facilitate a mutual understanding of the scientific and regulatory issues for their nanotechnology products.

With these points in mind, the FDA has issued guidelines describing its current thinking concerning regulated products containing nanomaterials or otherwise involving the application of nanotechnology. This guidance states that, based on its current scientific and technical understanding of nanomaterials and their characteristics, the FDA believes that evaluations of safety, effectiveness or public health impact of such products should consider the unique properties and behaviors that nanomaterials may exhibit [20].

In Europe, similar provisions exist for addressing combination products that may fall under more than one regulatory pathway. Since the primary mode of action may sometimes be difficult to determine for materials that exert an effect by virtue of novel properties arising at the nanoscale, determining the appropriate regulatory pathway(s) at an early stage of product development is of key importance.

In Europe, neither the Medicinal Products Directive nor the three Medical Device Directives (addressing medical devices, active implantable medical devices and in-vitro diagnostic medical devices, respectively) were originally drafted with nanotechnology in mind. The Medicinal Products Directive currently has no specific provisions relating to nanotechnology although a number of drugs containing nanomaterials have already been approved onto the European market. However, specific guidance on quality, toxicology, clinical development and monitoring aspects that have a bearing on nanotechnology are planned. Those developing drugs based on nanotechnology are strongly encouraged to interact with the relevant European Agency, the European Medicines Agency based in London which has an Innovation Task Force that addresses nanomedicine, from the earliest stages of development.

The European Medical Device Directives are based on broad “essential requirements” and the European Commission’s Medical Devices Experts’ Group has concluded that the provisions of the Directives broadly address nanotechnology-based medical devices. Essential requirements (ERs) of the Medical Device Directive [18]

that are of general relevance to any technology and which can therefore apply equally to products based on nanotechnologies include the following:

> *ER 1*: *The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.*
>
> *ER 2: The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order:*
>
> – *eliminate or reduce risks as far as possible (inherently safe design and construction),*
> – *where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated,*
> – *inform users of the residual risks due to any shortcomings of the protection measures adopted.*
>
> *ER 3: The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions…. as specified by the manufacturer. Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.*

Other essential requirements address aspects such as chemical, physical and biological properties; infection and microbial contamination; construction and environmental properties; devices with a measuring function; protection against radiation; devices with an energy source; and accompanying information.

Two key themes in essential requirements 1–3 are those of *acceptable risk* and the *reduction of risk*. As there are broad knowledge gaps concerning the risks of many manufactured nanomaterials and, in many cases, a poor understanding of their novel properties and mechanisms of interaction with the body, this subject becomes an extremely important one in terms of compiling relevant information for regulatory approval, and the active collection or generation of appropriate data concerning risk and safety an essential activity in developing nanomedical products.

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded in 2009 that a key limitation in the risk assessment of nanomaterials was the general lack of high quality exposure data both for humans and the environment. They noted that risk assessment procedures for the evaluation of potential risks of nanomaterials were still under development and could be expected to remain so until there is sufficient scientific information available to characterise the possible harmful effects on humans and the environment. They concluded that methodologies for both exposure estimations and hazard identification need to be further developed, validated and standardised [21].

A range of nanomaterial characteristics can give rise to novel hazards and their associated risks and these include particle size, shape, surface area, surface charge, surface chemistry, catalytic properties, solubility, crystalline phase, composition, zeta potential and other parameters. A useful overview of the issues surrounding the

risk assessment of manufactured nanomaterials is given in the Organisation for Economic Co-operation and Development's 2012 Report *Series on the Safety of Manufactured Nanomaterials No. 33* [22]. Furthermore, international standards are currently in preparation that are intended to address some of these needs, such as those in ISO/TC 229 *Nanotechnologies* [23].

For medical devices, the harmonised standard EN ISO 14971 [24] describes a systematic risk management process that can be used as the basis for identifying hazards; analysing, estimating and reducing risks; deciding on the acceptability of risks; providing for post-manufacturing risk review; risk communication and risk documentation. While not specifically addressing nanotechnology or nanomedicine, with the addition of data on hazards and risks arising from the nanoscale characteristics of materials, it may nevertheless provide a useful basis for addressing risks for many medical devices incorporating nanotechnology .

One particularly important conclusion of this brief regulatory review is that there are still data gaps concerning the safety of many manufactured nanomaterials and, in the case of highly-regulated product sectors such as nanomedicine, that there is an urgent need to characterise nanomaterials and identify novel hazards and risks that arise from their nanoscale properties. In many cases this may also have implications for the development of new measurement and test methods, particularly those that can contribute towards characterising the interactions between nanoscale materials and biological systems *in-vivo* for nanomaterials that may come into contact with cells and tissues. This will form an important part of compiling risk data that will be required for subsequent regulatory approval.

19.6 Health Technology Assessment

Health technology assessment (HTA) has been defined as "a multi-disciplinary field of policy analysis that examines the medical, economic, social and ethical implications of the incremental value, diffusion and use of a medical technology in healthcare" [25]. Health technology assessment works together with, and relies on, many scientific disciplines such as epidemiology, biomedical sciences, behavioural sciences, clinical effectiveness studies, health economics, implementation science, health impact analysis and evaluation. As in the case of reimbursement systems, HTA systems vary from country to country.

Health technology assessment is intended to provide a bridge between research and decision-making. It is a growing field and is intended to provide the data to support management, clinical, and policy decisions. It is also underpinned by the development of various disciplines in the social and applied sciences, especially clinical epidemiology and healthcare economics. Health policy decisions are increasingly seen as important as the risk of incurring substantial costs from making wrong decisions grows with the rising costs of providing treatment. Evidence-based data and cost-effectiveness information from HTA is therefore increasingly-used in many countries to underpin such decision-making.

In 2004, the European Commission and Council of Ministers identified Health Technology Assessment as a political priority and decided that there was an urgent need to establish a sustainable European HTA network. A European network, EUnetHTA, was established to "…help develop reliable, timely, transparent and transferable information to contribute to HTAs in European countries". EUnetHTA comprises government-appointed organisations from the EU Member States, EEA and Accession countries, together with various regional agencies and non-for-profit organisations that produce or contribute to HTA in Europe [26].

At the global level, the International Network of Agencies for Health Technology Assessment (INAHTA) was established in 1993 and has now grown to include 57 member agencies from 32 countries including North and Latin America, Europe, Africa, Asia, Australia, and New Zealand. All its members are non-profit making organizations producing HTA and are linked to regional or national government. At a national level, most countries have a range of organisations dedicated to developing and implementing HTA methodologies. Notable examples of such bodies include the National Institute for Clinical Excellence (NICE) in the UK, the Institute for Quality and Efficiency in Healthcare (IQWIG) in Germany and the Agency for Healthcare Research and Quality (AHRQ) in the US.

Griffin [27] suggests that access to many European markets, following regulatory approval of a healthcare product, is controlled or influenced by HTA agencies whose decisions depend heavily on value arguments informed by evidence on relative benefits compared with existing standards of care, and by economic modelling. While the regulatory decision to approve a product onto the market or not is based on a scientific judgement of its risks and benefits, the HTA decision, which often also influences whether a technology will be reimbursed or not, is a value judgement, although one based on scientific evidence and economic data. This has broad implications for medical technology companies, whether in the pharmaceutical, device or diagnostic sectors. The intention of healthcare services (e.g. the UK National Health Service) that use HTA is for it to help contribute towards the most effective use of limited resources.

Following a survey of stakeholders, Stephens et al. [28] found that the most common type of cost analysis in HTA is cost-effectiveness, with the primary methodology being decision models. Common end points included cost/life-years saved, cost/event avoided and cost/quality-adjusted life years (QALY). European HTA agencies generally have defined national guidelines they follow, while US agencies are less consistent in this respect.

The same report goes on to conclude that the use of different research methods and their conformity to published HTA principles varies significantly from country to country. Despite the study's relatively small sample size, the results suggest that HTA, using evidence-based medicine, will continue to rapidly evolve and will need standardized research methods and principles to guide assessment and decision-making around novel drug therapies, medical devices, and emerging technologies. It suggests also that a process for information sharing among HTA bodies may be needed to achieve this standardisation in research methods.

The quality-adjusted life year (QALY), as used by NICE in the UK [29], is a measure of disease burden, including both the quality and the quantity of life lived. It is used in assessing the value-for-money of a medical intervention under consideration. The QALY is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death. If the extra years would not be lived in full health, then the extra life-years are given a value between 0 and 1 to account for this.

The measure is then used in a cost-utility analysis to calculate the ratio of cost to QALYs saved for a particular health care intervention. This is then used to allocate healthcare resources, with an intervention with a lower cost to QALY saved ratio being preferred over an intervention with a higher ratio.

The measure is not universally accepted – some opponents suggesting that it means that some people will not receive treatment where it is calculated that the cost is not warranted by the benefit to their quality of life. However, its supporters argue that since healthcare resources are inevitably limited, the measure enables them to be allocated in the way that is most beneficial to society rather than to an individual patient.

This review makes no value judgement about the use of QALYs or other HTA methodologies. Rather, attention is drawn to the increasing application of health technology assessment around the world as a process used to justify expenditure on novel medical technologies, and one that will certainly be applied to the emerging field of nanomedicine. There is, therefore, a clear need for companies to generate data during product development that can contribute towards this process.

19.7 Reimbursement and Novel Medical Technologies

In the development of any new medical technology, attention needs to be paid at an early stage to how that product will be taken up and paid for by healthcare systems and providers. In Europe, the reimbursement and pricing of medical products is determined on a country-by-country, rather than European-wide, basis, leading to significant variations in systems, costs, and availabilities.

Many developments in nanomedicine may facilitate progress towards personalizing treatment towards individual patients. In a review of the reimbursement of personalized medicine products in Europe, on behalf of the Personalized Medicine Coalition, Garfield (2011) found significant differences in the ability of different country's reimbursement infrastructures to effectively assess and provide access to novel personalized medicine technologies [30]. The report suggested that, as a result, healthcare systems in many countries have been failing to appropriately evaluate and pay for personalized medicine technologies, with patients often being denied access to the most advanced drug and diagnostic treatments, while those healthcare systems continue to bear the costs of outdated trial-and-error approaches to medicine.

Inbar (2012) suggests that the clinical data required for regulatory approval does not necessarily encompass the clinical data required for successful reimbursement of a medical product and there are large differences also in terms of cost and effort between fitting into an existing reimbursement mechanism and developing a new code. He states, however, that, in many cases, the data required for the reimbursement process can be developed in parallel to the required regulatory data during the same clinical trials and that companies that consider regulatory and reimbursement as serial processes may reach the market with insufficient funds and time to finance another clinical trial just to develop reimbursement-related data. He concludes that reimbursement needs to be viewed as one of the issues that needs to be dealt with in parallel and early in the device development process, adding that some mistakes may be very difficult and expensive to correct later on [31].

19.8 Professional Uptake of Nanomedicine

At the 2008 conference *The Future Delivery of Medicine: 2020*, hosted at University College London (UCL), one key finding was that the potential benefits of a range of new medical technologies were being delayed by slow uptake in many European national healthcare systems. It was noted that healthcare budgets were under pressure across Europe while, at the same time, new developments in science and technology have emerged that could transform medicine. It was further suggested that delivering this potential in an affordable way will require healthcare to be more patient-centered and for medical professionals to think beyond their specialities and take a far more holistic view [32].

In addition, at a meeting before the start of the main conference, a group comprising speakers and other experts discussed potential guidelines for future policy formulation, including

- a need for changes across the value chain, from basic research through to delivery of medical care at the bedside and in the home;
- fundamental rethinking and reshaping of all the processes that currently underpin healthcare systems;
- challenging healthcare professionals to look outside their specialities;
- requiring regulators to rethink their views of risk and reimbursement authorities to take a different view of value and affordability.

The participants at the meeting also suggested that that there was a need for a new view of value and noted that, while advanced treatments may be expensive, they can lead to cost savings elsewhere and that health technology assessments need to take a broader view in the face of this new paradigm.

While nanotechnology, as an enabling technology, and a continually-evolving understanding of how nanomaterials and biology interact at the nanoscale is beginning to revolutionise medicine and medical products in areas such as screening,

prognosis, diagnosis, treatment planning, therapy, follow-up, and translational research, there is at present limited training available on nanomedicine, both within the curricula at medical schools and at a professional level thereafter.

A 2010 proposal to the European Commission's Directorate-General (DG) Research and Innovation Health Directorate by the European Alliance for Medical and Biological Engineering and Science (EAMBES) [33] suggested that the medical world could potentially become confused by the breadth and depth of the possible emerging medical technology interventions available. As a result, non-suitable solutions could be adopted that do not have the expected impact and thus do not constitute the correct way to approach the issue of preparing a framework for innovative therapeutic approaches. It suggested that this situation had already caused a number of problems in relation to the actual uptake of medical technology research and products resulting in a lower than expected synergy between the biological and medical engineering (BME) industry and the health sector.

The proposal went on further to suggest that a major impeding factor in the adoption of novel medical technology products is that they imply changes not only on the way the doctor thinks but also changes in the medical organizational and regulatory frameworks.

Many novel medical technologies have the potential to change the way medical practice is organised. Currently, typical diagnostic tests conducted by a General Practitioner might comprise taking a blood or bodily fluid sample from the patient, labelling and packaging it, sending it away to a central laboratory facility, waiting for several days for the results to come back and then recalling the patient to the surgery for a further consultation, discussion of the results of the tests and treatment. This multi-step procedure could potentially be replaced in the future by the use of a "smart" diagnostic device, designed for application in a variety of disease or metabolic tests, based on nanobiosensor and microfluidic technologies, and capable of being used in a GP's consulting room and of giving accurate results in a couple of minutes. Such novel diagnostic devices are currently in development and would, in all probability, be welcomed by GPs but there are a number of potential implications such as:

- diagnosis is changed from a remote dedicated laboratory facility/expert to a local "smart" device/medical generalist;
- while there may be costs in implementing such a technology, costs elsewhere, such as handling/packing/transport and laboratory costs would be minimized;
- long-established and familiar procedures would be changed;
- as diagnostic results could be immediately available, there would be implications for both GP, perhaps in terms of training on the interpretation of data and subsequent actions, and for patient;
- issues of trust in the quality and reliability of diagnostic data.

Therefore, in addition to the technological development of the device itself, attention needs to be paid to a broad spectrum of issues such as: the way and situation in which it will be used, e.g. by a patient at home, by a field worker or paramedic, by a qualified nurse, at a generalist's surgery or by a specialist at a hospital; whether

existing practice or organisational aspects are altered; what implications this has for training, interpretation of results and consequent actions; impacts on costs and cost points; storage of confidential data; and many other aspects.

It is important, therefore, for researchers and companies to work with medical professionals at an early stage of product development. Nanomedicine, in particular, has implications for implementation by medical professionals as it utilizes properties of materials that manifest at the nanoscale and which may not be readily apparent or understood, or addressed in their training. Furthermore this understanding of the principles of nanomedicine by medical professionals is important as they form a key and trusted route of communication to patients.

19.9 Public Perception

Usually, the general public, as patients, will first come into contact with nanomedical products via medical professionals, with whom there is generally a high degree of trust and which, again, reinforces the importance of building relationships and trust with the medical profession during development of the product, as previously discussed.

The public's own perception of emerging technologies may be, however, influenced by previous scientific debates or controversies, such as "Mad Cow" Disease (bovine spongiform encephalopathy) (nvCJD), GMO foods, contaminated blood, etc., and how these have been represented, or misrepresented, in the popular media. The public cannot be expected to fully perceive and understand scientific risks arising from new technologies. The same public, however, are perfectly happy to take a risk/benefit decision where they broadly understand the factors involved and perceive the expected benefit as outweighing the risk, e.g. crossing the road, driving a car or travelling by air, or to choose one risk over another ("the lesser of two evils"). Many medical treatments are known by the public, as patients, to involve some measure of risk, e.g. X-rays or aggressive chemotherapy, but they are prepared to undergo such procedures as they perceive the benefits to be gained as outweighing those risks and trust those professionals that carry out such procedures.

The perception of a risk amongst the general public can vary greatly depending upon factors such as:

- the cultural, socio-economic and educational background of the person(s) involved
- whether exposure to the hazard is
  - involuntary;
  - avoidable;
  - from a man-made or natural source;
  - due to negligence;
  - arising from a poorly understood cause;
  - affecting a vulnerable group within society;
- whether there is an obvious benefit to be gained from exposure to the risk.

Furthermore there may be a tendency to distrust "big industry" in some sectors where profits may be seen to outweigh safety concerns. All of these factors taken together may colour attitudes towards the acceptance of new technologies, especially if there has been poor communication about them.

Kahan and co-workers (2007) carried out a study amongst a recruited sample of United States subjects to assess their opinions about nanotechnology [34]. The responses of 1,500 subjects not exposed to additional information suggested that Americans were largely uninformed about nanotechnology: 81 % of subjects reported having heard either "nothing at all" (53 %) or "just a little" (28 %) about nanotechnology prior to being surveyed, and only 5 % reported having heard "a lot." Nevertheless, most of the same group of subjects, 89 %, were reported as having an opinion on whether the benefits of nanotechnology outweigh its risks or vice versa with slight majority (53 %) appearing to view benefits as outweighing risks. When subgroups were examined, however, more divisions were revealed. Men (59 % to 36 %) were significantly more likely than women (47 % to 40 %) to think that risks outweigh benefits. Moreover, whereas a majority of whites (54 %) believed that benefits outweighed risks, 49 % of African-Americans of viewed risks as outweighing benefits. White males were the most pro-benefit orientated (61 % to 30 %).

The study also backed up conclusions from previous studies that *affect* (a person's positive or negative emotional orientation) is one of the most powerful influences on individuals' perceptions of risk – subjects in the survey were asked to indicate whether nanotechnology made them feel "very bad," "bad," "neither good nor bad," "good," or "very good." Furthermore the study suggested how people react to information depends largely on their *values*. One of the major findings was that dissemination of scientifically-sound information is not by itself sufficient to overcome the divisive tendencies of cultural cognition. The authors concluded that those in a position to educate the public, including government, scientists and industry, need also to intelligently frame that information in ways that make it possible for persons of diverse cultural orientation to reconcile it with their values.

A later study by Bottini and colleagues (2011) amongst 790 citizens chosen randomly from four different urban areas of Rome reported that those surveyed exhibited optimism towards nanomedicine despite low awareness of currently available nanodrugs and nanocosmetics, and limited understanding of biocompatibility and toxicity aspects. The study concluded that, if such public optimism justifies the increase in scientific effort and funding for nanomedicine, it also obliges toxicologists, politicians, journalists, entrepreneurs, and policymakers to be more responsible in their dialogue with the public [35].

While there would seem, therefore, to be no major widespread prior distrust of the application of nanotechnology to medicine despite concerns in other areas of technology there is, nevertheless, a need for clear information to be made available to the public and other stakeholders about the benefits and risks of nanomedicine in a language that can be clearly understood and through channels that are trusted.

19.10 Ethical Considerations and Safeguards

While an in-depth review of many of the potential ethical issues associated with nanomedicine is provided by Donald Bruce within this book, it is nevertheless useful to consider some key points here as part of an overview of the challenges facing its widespread implementation.

19.10.1 What Do We Understand by Healthcare?

The increasing ability that we have to manipulate matter precisely at the nanoscale, combined with our improved understanding of biology, may influence our perception of what medicine and what a well person is, e.g.

- Just the treatment of disease?
- The correction of any deviation from what is considered "normal" function?
- What do we mean by "well" if we will be able to monitor at so many levels?
- What is the borderline between impaired function correction and performance enhancement?
- What are the expected limits of a "cure"?

While most people would probably accept the use of medicine for treatment of a disease or the correction of a physiological condition or impairment, they may not readily accept its application for enhanced performance, e.g. strength, senses, endurance for sports, military or other non-medical purposes.

19.10.2 The Changing Face of Medicine

Over the past several centuries medicine has changed beyond all recognition from the seventeenth century where treatments were largely palliative with the doctor focusing mainly on nonphysical supportive measures, through the development of hospital medicine in the nineteenth century and "laboratory medicine" in the twentieth century to the current twenty-first century scenario where we are now beginning to understand the human body as an intricately structured machine with billions of complex interacting parts, with each part (and each subsystem of parts) potentially subject to individual investigation, repair, and possibly replacement by artificial technological means. Along with this transformation of medicine over the centuries, the role of the medical professional has also changed enormously and we might reasonably expect medicine to become even more technological. But do good scientists or engineers make good doctors?

19.10.3 A Data Overload?

The development of novel diagnostic and imaging technologies, coupled with advances in genomics, proteomics and metabolomics (now commonly referred to collectively as the "-omics") means that there is a huge amount of data becoming available to medical professionals. This begs important questions such as

- Who can interpret all of this data?
- How much of the information is clinically significant?
- Who does the data belong to? The healthcare provider? The patient?
- How will the data be stored and transmitted safely?
- Where will the data be stored?
- What about patient confidentiality issues?
- What about the patients right to *know* and, equally, *not to know* certain information?

One particularly important element is maintaining the confidentiality of medical data… much of it could be of value to third parties other than the patient and doctor, e.g. employers, the government and commercial organisations such as insurance companies.

A study by Erlich and colleagues (2012) at the USA's Whitehead Institute demonstrated that the supposedly confidential names of research study participants could be traced from de-identified genetic data [36]. The researchers identified nearly 50 men and women who had submitted samples and had their genomes sequenced for a study performed by the Center for the Study of Human Polymorphisms (CEPH).

By matching short tandem repeats that they found on the Y chromosomes of men in the CEPH study to Y-STRs in publicly-available genetic genealogy databases, the researchers were able to recover the family names of men in the CEPH dataset who had submitted their Y-STRS to these repositories. With this information, they searched other free online information sources including record search engines, obituaries, genealogy websites, and public demographic data from the National Institute of General Medical Sciences' Human Genetic Cell Repository, housed at the Coriell Institute, and were able to track down the participants.

This study suggests that it may be difficult in practice to guarantee the security of medical and genomic data and that there is a need to balance research participants' privacy rights with the societal benefits to be realized from the sharing of biomedical research data.

19.10.4 Non-discrimination and Equity

Non-discrimination is a widely-accepted principle that people deserve equal treatment unless there are reasons that justify difference in treatment. In this context it primarily relates to the distribution of healthcare resources. Equity is the ethical principle that everybody should have fair access to the benefits under consideration.

Earlier commentary indicates, however, that access to treatment may vary from country to country because of regulatory, health technology assessment and reimbursement issues and, within some countries, access may even vary between different regions due to differing practices, priorities or availability of resources.

19.10.5 The Precautionary Principle

This principle entails the moral duty of continuous risk assessment with regard to the not fully foreseeable impact of new technologies. While the Precautionary Principle is already enshrined within European legislation, there are concerns from some quarters that could it be used as the justification to block potentially life-saving technologies on the grounds that the science is not yet fully understood.

19.11 Training

In formal medical education, very few medical schools currently offer modules on nanomedicine as part of their curricula. At the same time, massive levels of investment into research on the application of nanotechnologies to medicine, at both academic and commercial levels, means that there are increasing numbers of products incorporating nanotechnology appearing on the market with many more in the product pipeline or at the stage of clinical trials or awaiting regulatory approval.

While an increasing number of universities are now offering nanotechnology-based undergraduate or postgraduate level courses, there are still only a limited number specifically addressing nanomedicine or specific medical disciplines with a significant medical nanotechnology component.

At a professional level, organisations such as such as the Institute of Nanotechnology (IoN) and universities such as Cranfield and Oxford have developed short courses aimed at addressing training needs in nanomedicine and the application of nanotechnology to topics such as medical diagnostics, imaging, drugs and biosensors, as well as nano- risk and safety issues. These have attracted interest from a range of participants including those working in academia and research, industry, medical professionals and medical students, healthcare providers and regulatory authorities.

The successful adoption and implementation of nanomedical solutions in the clinic will depend on the presence of informed decision-makers who understand the underlying science, opportunities and benefits that the technologies can bring, short and long terms costs and savings, and how nanomedicine can be integrated safely and effectively into everyday healthcare. This includes those working in research funding, commercial strategy, regulatory affairs, health technology assessment, reimbursement and healthcare provision professionals, insurers, and amongst the medical professions. There is, therefore, an ongoing need for training in nanomedicine at both academic and in-service, professional levels.

19.12 Conclusions and Perspectives for the Future

This chapter intends to highlight some of the non-technical challenges that researchers and developers are likely to face in bringing medical products based on nanotechnology to the market and clinic. Many of these challenges are not exclusive to nanomedicine but apply generally to emerging medical technologies. However, some of these challenges may be compounded by the fact that nanoscale materials frequently exhibit novel properties that can provide both benefits and opportunities but that, at the same time, may present novel hazards and risks that are poorly understood. Characterisation of novel nanomaterials and the establishment of a widely-available repository of safety data will therefore be vital to the success of nanomedicine.

From the author's personal experience, the attitude towards nanomedicine from a wide variety of stakeholders who have attended professional training courses, workshops and conferences on the topic, including medical professionals, regulators, industry professionals and others, has been positive. There, however, remains a widespread lack of awareness on the subject in the wider medical community and much needs to be done to engage with these professionals to impart knowledge, build trust and promote the uptake of novel nano-based products.

It is also clear that better communication is needed with health technology and reimbursement professionals. In healthcare systems where cost containment is increasingly critical to healthcare delivery, it must clearly be demonstrated that nanomedicine can deliver better treatments while reducing costs in the short, middle or long term, for example by earlier or more accurate diagnosis, more effective treatments, or by reducing lengths of stay in hospitals. In addition, there is clear scope for a contribution towards more personalised form of medicine rather than a one-size-fits-all approach, although this may well necessitate the development of new business and professional practice models.

Because of the comparative timescales required for regulatory approval, it is likely that the fastest progress to market for nanomedicine will be seen in the areas of diagnostics, biosensors and other medical devices. However, developments in the pharmaceutical and regenerative medicine sectors, although possibly longer term, are likely to be significant and potentially disruptive in terms of contributing to new paradigms of treatment.

In the longer term, there is also potential for massive synergy between nanomedicine and other emerging field such biomimetics, particularly in terms of integrating nano- and biological structures for biosensing, drug delivery and regenerative medicine, and designing new generations of novel nano-based devices.

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