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TOWARD NEW MODELS FOR INNOVATIVE GOVERNANCE OF BIOMEDICINE AND HEALTH TECHNOLOGIES

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FOREWORD

Governments are seeking to ensure that they develop and maintain the appropriate governance frameworks for biomedical and health innovation. The rapid pace at which scientific and technological advances take place in the life sciences, combined with the complex and heterogeneous nature of the knowledge within biomedical innovation across multiple fields and subfields, makes this a very challenging area for regulators and policy-makers. In addition, within biomedical and health innovation there is a wealth of research and clinical data that needs to be captured and combined to inform the research policy, regulatory and healthcare communities. Of the many significant challenges for the governance of this sector, perhaps the greatest is seen in the creation of the right conditions to best support the translation of biomedical innovation to the point of care.

This report draws on previous work of the OECD Working Party on Biotechnology (WPB) that addressed new models of governance for biomedicine and health innovation, for example, work on the governance of pharmacogenetics and biomarkers. In large part, it has been informed by the discussions at the OECD workshop on "Better Health through Biomedicine: Innovative Governance" that was held in Berlin, Germany in September 2010.

The current report examines examples of new and emerging governance models that aim to support the responsible development of diagnostics and treatments based on the latest advances in biomedicine. In particular, it presents programmes and initiatives that aim to manage uncertainty in the development and approval of new medical products and thereby to improve the understanding of the risk/benefit balance. The report also identifies some of the main challenges for policy makers, regulators and other communities involved in the translation of biomedical innovation and health technologies from the laboratory bench to point-of-care.

The report first focuses on the specifics of governance in important areas of biomedical research: biomarkers for personalised medicine; bio-nanotherapeutics; and therapies derived from stem cells. The report then considers the more general challenges that affect translational research (i.e. research that makes basic science applicable to the clinical situation) and the decision-making process for market approval of new medical products. It concludes by highlighting the main policy challenges raised by the governance of biomedicine and by suggesting areas of possible improvements to facilitate a more efficient translational research environment and reduce the time-to-market for regulated products.

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EXECUTIVE SUMMARY

Governments are facing increasing pressure to adapt current governance frameworks for biomedical and health innovation to the rapidly evolving research and development environment in the field. The pace of scientific and technological advances in the life sciences, the complexity and heterogeneity of the knowledge relevant to biomedical innovation across multiple fields and subfields and the need to integrate vast amounts of research and clinical data all combine to create significant challenges for the governance of this sector, perhaps the greatest of which is the challenge of creating the conditions that can best support the transfer of biomedical innovation to the point of care.

The OECD Working Party on Biotechnology (WPB) has for some time been looking at models of governance for biomedicine and health innovation, with a particular focus on systems to support the safe, efficient translation of biomedical innovation and health technologies from the laboratory bench to the patient. In particular, the OECD WPB staged a workshop in Germany in September 2010 on "Better Health through Biomedicine: Innovative Governance", the discussions at which have informed this report.

This report looks at some of the specifics of governance in three important areas of biomedical research: biomarkers for personalised medicine; bio-nanotherapeutics; and therapies derived from stem cells. Whilst these biomedical diagnostics and therapies are comparable to conventional ones in some respects, a number of new challenges sets them apart and impacts on the ability of decision-makers to make appropriate, well-informed decisions. The main challenges for policy in this area are:

- **Extensive data management –** Vast amounts of both scientific and clinical data are generated in the field and need to be integrated into the decision-making processes for diagnostics and treatments. The main difficulties here are, firstly, in determining what data are required by regulators; secondly, in establishing mechanisms to obtain, share and pool the data; and, finally, in creating the necessary systems to analyse the data.

- **Validation and standardisation –** In emerging fields, such as bio-nanotechnology and the use of stem cells, a significant bottleneck is the lack of internationally agreed norms and standards. For example, the range of options for sourcing stem cells complicates the development of stem cell-derived therapies, particularly when these are tissue-based. So far, standardisation in this field has largely emerged through the self-regulating mechanisms of scientific practice. This issue is now also being addressed through standards and protocols in areas including product development, regulation, storage and traceability.

- **Balancing risk and benefit given limited knowledge and an environment of uncertainty –** Given the pace of discovery in the fields of biomedical and health innovation, new products or procedures may reach regulators while the available information on them may still be incomplete and insufficient to enable regulators to make entirely evidence-based decisions. Early consultation is becoming an indispensable means of maximising the amount of information available to regulators. Innovators often hold more and better information than regulators in relation to at least some kinds of technical and scientific developments.

- **Timely public engagement and communication –** Biomedical innovation creates challenge with respect to risk, equity, privacy, confidentiality, human dignity, right to life and freedom of research. This makes for a particularly complex environment for decision-makers and the public alike, necessitating special efforts in communication and consultation.

- **Converging technologies, combination products and multi-functionality –** The distinctions between different forms of medical products, such as drugs, diagnostics and devices, are becoming blurred. Combination products fall between regulatory regimes (e.g. regulation of medical devices, of drugs and of food) and thus require novel regulatory approaches.

- **High costs and relative effectiveness** – Decisions about where to place resources are difficult in all complex technological fields and therefore in most areas of biomedicine and health. The dilemma is clearly illustrated in personalised medicine in which some highly effective treatments relevant to relatively few patients may be available only at very high cost.

- **Evolving business models and industry engagement –** The opportunities presented by bio-nanotechnologies, stem cells and personalised medicine are significant. Industry is playing a crucial role in the translation of these technologies to the patient, necessitating the sharing knowledge and experience with the other communities involved. One challenge will be to better understand and adapt governance frameworks to new emerging business models.

Many of the above challenges are not unique to any one specific field but may be magnified in certain areas depending on how a new therapeutic product is applied and in what context. It is important to distinguish in each case which challenges are due to incomplete or uncertain scientific knowledge and which to specific social and/or economic factors. A growing challenge for regulators, for example, is to be able to balance the need for rapid access to innovative therapies with the need for comprehensive data on their benefits and risks.

There is a variety of views today about what changes to existing frameworks and regulatory systems are necessary to facilitate the translation of this wave of new biomedical and health innovations from bench to bedside. National and regional strategies aimed at developing new governance and regulatory models are emerging across the OECD area and elsewhere. Governance frameworks that promote greater collaboration across all relevant stakeholders can help to realise the opportunities presented by biomedical innovation.

The report shows that a range of new collaborative and integrated approaches to governance and regulation is gradually emerging in a number of countries and regions in response to the rapid evolution of biomedical technologies. Multi-stakeholder partnerships and collaborations across sectors are gaining influence. These partnerships are *de facto* encouraging a wide-range of new norms of behaviour and are evolving into subsystems of governance in such diverse areas as product coverage, licensing, standard-setting and risk management.

SECTION I: GOVERNANCE CHALLENGES: ILLUSTRATIVE TECHNOLOGY-BASED EXAMPLES

Research in biomedical and health innovation has advanced rapidly since the early biotechnology discoveries of the mid-1970s. It has generated knowledge, tools and techniques that have vastly improved the drug research process. Despite the tremendous advances in knowledge and technology, many developments remain "emergent" in the sense that they have not yet been translated or fully integrated into healthcare systems and medical practice.

This section considers examples of three core developments in biomedicine - biomarkers for personalised medicine; bio-nanotechnologies; and stem cells - identifying in each case, the main policy and/or regulatory issues associated with the technology. These developments and technologies are used as examples to identify governance factors that may influence the diffusion or uptake of biomedical therapies and products and thereby affect the further progress of the sector.

The section shows that the governance of translational and clinical research and the transfer of safe and efficient biomedical innovation from bench to bedside – with all the technical, regulatory, social and economic issues that it might raise – is a critical challenge. The decision-making processes used in translational research and market approval are complex and involve multiple stakeholders. They take place in an environment of scientific and technical uncertainty with respect to the application of biomedical innovation and new health technologies at the point of care.

Personalised medicine and the role of biomarkers

Personalised medicine aims to provide care tailored to address specific patient characteristics such as the susceptibility of an individual to a disease or their response to a drug. It is based on new methods of molecular analysis which can lead to more accurate and targeted diagnoses and treatment. As defined by the United States President's Council on Advisors on Science and Technology, "Personalised Medicine" refers to "the tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into sub-populations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not" (PCAST, 2008). Personalised medicine offers new possibilities for the management of medical conditions.

The adoption of personalised medicine into clinical practice largely depends upon the discovery and validation both of biomarkers of pathogenic conditions and of biomarkers associated with a pharmacologic response to a drug. Biomarkers are defined as "measurable characteristics that reflect physiological, pharmacological or disease processes" according to the European Medicines Agency (Biomarkers Definitions Working Group, 2001), and they can be of different forms: genomic, transcriptomic, proteomic and metabolomic biomarkers (all of which are termed molecular biomarkers) and imaging biomarkers.

Imaging biomarkers are increasingly assuming a significant role in diagnosis and monitoring often without requiring physically-invasive investigation. Several characteristics of imaging biomarkers set them apart from molecular biomarkers. Non-invasive imaging has been in routine use for diagnosis and disease management for several decades, and the ability to identify a wide spectrum of patho-physiology using imaging methods is well established. Imaging also offers tremendous versatility for the continuous,

structural and functional assessment of therapies, e.g. by offering snapshots of the bioactivity of drug compounds over time. The use of imaging biomarkers is, therefore, increasingly viewed as one of the most powerful low-cost means to measure and monitor the effects of a drug or device.

Proteomic and genomic biomarkers are the two types of biomarkers at the forefront of research today. The first is of importance because the majority of current drug targets are proteins and therefore most biomarkers used in clinical studies are based on proteomic applications. The importance of the second results from advances in genomic technologies and large scale data management. Notably, the development of Genome-Wide Association Studies (GWAS) has enabled significant progress to be made in the discovery of gene candidate biomarkers, making it a particularly powerful potential tool for determining the genetic components, and related protein-related mechanisms, of complex multigenic and multifactorial diseases (see Box 1).

Box 1. Genome-wide association studies

A Genome-Wide Association Study (GWAS) involves rapidly scanning for biomarkers across complete sets of the DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations have been identified, researchers can use the information to develop better strategies to detect, treat and prevent the disease under scrutiny. Such studies are particularly useful in finding genetic variations that contribute to common, complex diseases, such as asthma, cancer, diabetes, heart disease and mental illnesses.

To carry out a genome-wide association study, two groups of participants are required to undertake a so-called case-control study: people with the disease being studied and similar people without the disease. Researchers obtain DNA from each participant, usually by drawing a blood sample or by rubbing a cotton swab along the inside of the mouth to harvest cells. Each person's complete set of DNA, or genome, is then purified from the blood or cells and scanned using automated laboratory machines. The machines quickly survey each participant's genome for strategically selected markers of genetic variation, which are called single nucleotide polymorphisms (SNPs).

If certain genetic variations are found to be significantly more frequent in people with the disease compared to people without the disease, the variations are said to be "associated" with the disease. The associated genetic variations can serve as powerful pointers to the region of the human genome where the disease-causing factor resides.

However, the associated variants themselves may not directly cause the disease. They may just be "tagging along" with the actual causal variants. For this reason, researchers often need to take additional steps, such as sequencing DNA base pairs in that particular region of the genome, to identify the exact genetic change involved in the disease.

Source: www.genome.gov (accessed April 2013)

Within the clinical setting, biomarkers can be of use at all stages of disease characterisation and/or disease and therapy management. In terms of drug discovery, the identification of biomarkers of a disease is a fundamental step in finding new potential therapeutic targets. In recent years, an important advance has been made through the development of combination products that, based on biomarkers, enable the prediction of the response of an individual to a particular drug. Efforts to improve cancer therapy have led the way in the development of these combination products (Box 2).

Box 2. Oncology has led the way in the use of biomarkers

Vast amounts of data from various molecular profiling studies have been used to facilitate a shift away from conventional, broadly-based therapeutic approaches to cancer, towards more tailored strategies. The expansion of personalised treatment protocols now depends on the development of robust, well-validated, informative predictive and pharmacodynamic assays. The story of Herceptin® and HER2 offers an early example of the use of predictive biomarkers in breast cancer.

Herceptin® is a therapy for women who have metastatic breast cancer and whose tumours express too much of a protein known as HER2. Approximately one in four women with breast cancer test positive for HER2, a consequence of their genetic make-up. By using HER2 as a genetic biomarker to test all women with breast cancer, it is possible to identify and treat those who will benefit from treatment with Herceptin®. By only using Herceptin® in this targeted manner, the observed effectiveness of Herceptin® is increased. In effect, the percentage of women who will respond to the treatment is larger within the targeted group, as compared to the percentage that would benefit if the treatment were given across the whole population of women with breast cancer. This targeting approach can increase the overall effectiveness of a fixed number of treatments and thereby change the risk-benefit ratio for treatment - as the medicine is prescribed only to women who are likely to benefit, the number of patients who experience side effects (or experience no therapeutic effect) is significantly reduced. Herceptin® is the first success story for a personalised medicine, with sales of USD 747 million in 2005. Since 2005, about 15 personalised drugs and their companion tests (also called pharmacogenetic tests) have reached the market.

Sources: Hamilton DP (2006), Genentech's Profit Jumps 64% on Strong Cancer-Drug Sales, Wall Street Journal (Eastern edition); Issa A.M. (2007), Personalise Medicine and the Practice of Medicine in the 21st Century, Journal of Medicine, Vol.10, Issue 1, pp. 53–57, see www.ncbi.nlm.nih.gov/pmc/articles/PMC2323540/

However, there are still significant challenges in the discovery and validation of biomarkers. Those challenges are mainly inherent to the complexity of biological systems and the difficulty in understanding the pathogenic processes that lead to a particular disease.

Governance challenges in personalised medicine and the use of biomarkers

Challenges associated with the governance of innovation in personalised medicine and the uses of biomarkers include:

- **Achieving good and adaptive connectivity throughout the value chain** bringing innovative biomarkers and associated medical technologies from the laboratory bench to point-of-care. Numerous efforts at both national and international levels aim to support the discovery of biomarkers and their safe and efficient application in the clinical setting. Some of these initiatives are focused on creating the specific infrastructure and necessary organisation of research, while others are focused on platforms for data generation, exchange and development, including collection of clinical samples, data management infrastructure and execution of GWAS studies. Large research networks are being developed, as well as innovative partnerships based on consortia involving both public and private entities. These collaborative initiatives go far beyond what any one stakeholder group (e.g. academics, industrialists, physicians and regulators) could do alone.

- **Maintaining good governance in a changing environment of innovation in personalised medicine**. Questions remain as to what governance frameworks, oversight mechanisms, infrastructures and organisational changes, including regulatory and institutional innovation, will be required to support the most effective implementation of the technological developments associated with biomarkers and personalised medicine, in particular for combination products.

Consideration is given below to some of the collaborations being established to enable engagement and enhance efficiency in biomarker discovery; and to some of the challenges of policy-making and regulation in an environment of uncertainty.

Achieving good and adaptive connectivity throughout the value chain

Biomarkers must be demonstrably fit-for-purpose. The road from characterising biomarkers to validating them for a specific use and applying them to patient diagnosis, screening and therapeutic intervention is both long and fraught with difficulties. Assessing the analytical and clinical performance of biomarker-based diagnostic assays for use in clinical practice or medical product development requires large-scale studies. Setting these up can be time-consuming and costly. Innovative knowledge-sharing mechanisms and new development approaches have proved useful in assessing a growing number of candidate biomarkers and in overcoming these challenges.

Innovative pre-competitive consortia can help to foster rapid innovation in early stage research, such as for biomarker validation, and may help to avoid or reduce patent thickets[1] or anti-commons[2] which have the potential to deter innovation. By sharing knowledge about failures, or know-how about regulatory procedures, development costs can also be reduced. Pre-competitive consortia can be useful in helping researchers and companies to manage uncertainty in the development of medical products. It has been demonstrated that such pre-competitive collaboration offer a feasible, robust approach that encourages discovery and can accelerate the translation of biomarkers into clinical practice. Governments across OECD countries are actively engaging with companies to support the discovery and development of biomarkers through the establishment of a host of public-private partnerships. A few examples of these initiatives are outlined in Box 3.

Box 3. Examples of consortia for biomarkers discovery and validation

The Early Detection Research Network (EDRN): Established in the United States in 2000, the aim of the EDRN is to foster the discovery and validation of clinically useful biomarkers for cancer detection, diagnosis and risk assessment. It is an investigator-driven consortium of more than 200 investigators and 40 laboratories structured around four major science-based components: Biomarker Development Laboratories; Biomarker Validation Laboratories; Clinical and Epidemiologic Centres; and a Data Management and Coordinating Centre (DMCC). A steering committee, comprised of principal investigators is responsible for overall oversight. The DMCC provides logistics support, conducts research into statistical methodologies and manages and analyses data for the consortium. EDRN promotes the transfer of discoveries at the laboratory bench to applications at the bedside. Its novel systematic approach to biomarker validation (outlined in Table 1) has been adopted by many other programmes in the United States and internationally. The process takes the research through five phases, progressing from the earliest stages of research (identification of promising directions) to the point at which a biomarker can be used in broad populations. As research moves through the phases, the evidence for the clinical usability of the biomarker increases.

The FNIH Biomarker Consortium: the Biomarker Consortium3 was established by the Foundation for the National Institutes of Health (FNIH) in 2006 as a public-private partnership. The consortium includes US government agencies; industry; and patient advocacy groups and other non-profit private sector organisations. Sponsors and founding members include: the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Industry Organisation (BIO) and the Centres for Medicare and Medicaid Services (CMS). The Consortium has to date strategically focused on four high-impact areas: cancer; inflammation and immunity; metabolic disorders; and neurosciences. It acts as a hub for biomarker data and knowledge generation and as a grant provider, stimulating the submission of concept protocols by researchers. The consortium further promotes pre-competitive research and development for novel biomarkers by making its project results publicly available.

Table 1. Process for the development and validation of future biomarkers (adapted from EDRN)

Preclinical Exploratory	Phase 1	Promising directions identified
Clinical Assay and Validation	Phase 2	Clinical assay detects established disease condition
Retrospective Longitudinal	Phase 3	Biomarker detects preclinical disease and a screen positive rule is defined
Prospective Screening	Phase 4	Extent and characteristics of disease detected by the test and the false referral rate are identified
Disease Control	Phase 5	Impact of screening on reducing burden of disease on population is quantified

Maintaining good governance in a changing environment of innovation in personalised medicine

In order to both capture the benefits of biomedical research and to ensure its safe and responsible use, the need for policy and regulatory intervention is moving to ever earlier stages of technological and product development. This is particularly the case in the responsible and effective use of biomarkers, which are central to the development of many new diagnostic and therapeutic products. Both the policy and regulatory communities are working in an environment of uncertainty. They need to take decisions that address the urgent necessity for safe and efficient diagnostics and therapeutics for certain diseases in the face of knowledge-gaps about the biological processes at the origin of those diseases.

Balancing of risk and benefit within the context of limited knowledge and uncertainty is at the core of biomedical innovation management. Several organisations have been working on developing guidance to support regulatory institutions in their decision-making process for validating new biomarkers (e.g. the International Conference on Harmonisation and the Office of Public Health Genomics at the US Centres for Disease Control (CDC)), but significant challenges remain. Policy-makers and regulators need to know, for example, whether a novel clinical test or therapy is beneficial and whether it will improve healthcare outcomes; what the potential cost of delivery is; whether there will be significant economic benefits, e.g. benefits within healthcare system and beyond; and what operational changes will be required in order to deliver the benefits. Timely and early-stage consultation is becoming an indispensable means of gathering information to support policy formulation.

To these operational challenges are added the potential social and ethical implications of developing new diagnostic tests, in particular when these tests are predictive or aim at an early diagnosis of the disease. For example, while data generated by GWAS studies may result in the discovery of candidate genes which can be used in diagnostic tests to identify an association between a genetic profile and the development of a disease, there is no guarantee that a treatment will be available. Thus, while it may be possible to use biomarkers to identify people likely to develop Alzheimer's disease in the next two, ten or twenty years, this can currently only lead to the use of measures to prevent and monitor the disease, no efficient treatment for the Alzheimer's disease currently being available.

Another issue is how to recoup the investment in these new technologies. Regulatory agencies have yet to formulate consistent payment structures for high-investment, high-value tests, some of which promise to revolutionise healthcare and reduce costs. Biomarker tests that, for example, identify which patients will be most likely to respond to specific treatments hold the promise of improved health outcomes for the patient and efficiency gains for healthcare systems. However, the financial gains from these

improvements are not generally returned to the diagnostic company. Across OECD countries, the pricing and reimbursement for diagnostic tests is essentially cost-based. Reimbursement does not reflect the clinical value the test might bring to the patient or its associated economic value to the healthcare system. This lack of recognition of the benefit of testing within pricing and reimbursement mechanisms represents a genuine disincentive to the industry to engage in development of new biomarker assays.

Decisions on coverage (i.e. how many and which patients are tested) are often based on two determining factors: *i)* that the test has proven its validity and utility in clinical care: and *ii)* its predicted value to the health system (typically based on comparative cost-effectiveness). Reliance on the latter, positive health outcomes, is often a primary factor in deciding coverage. Randomised clinical trials (RCT)s − today's gold standard for producing scientific evidence on the benefit/risk profile of therapeutic interventions - are not a trivial undertaking, are difficult to set up for biomarkers and are often inconclusive. The merits, disadvantages and feasibility of RCTs have become a central issue in the debate among policy-makers and researchers about what constitutes valid and reliable evidence for evaluating biomarkers.

Some biomarker tests also require long timeframes and a large population base in order to establish health outcomes. The true economic value of these tests may therefore not be known for a very long time even when they have been seen to be diagnostically accurate. Alternative approaches, including case-control[4] and cohort[5] studies can be useful in accumulating evidence on the validity and clinical effectiveness of using biomarkers.

Biomarkers are posing governance and regulatory challenges in the area of personalised medicine. Challenges are also seen in the application of bio-nanotechnology.

Health and biomedical applications of emerging bio-nanotechnologies

Nanotechnology is an emerging technology, that appears to be converging with ICT and biotechnology, and that may have characteristics of a "general purpose" technology. It has the potential to significantly affect the productivity and growth of a range of both established and new companies and industries. Its combination with biotechnology is expected to result in breakthrough innovations and bio-nanotechnology may play a fundamental role in many sectors. Major impacts from bio-nanotechnology are foreseen in healthcare. Novel, integrated governance and regulatory models are now emerging to ensure the responsible development, distribution and use of a new wave of products based on bio-nanotechnology.

A few examples of applications of bio-nanotechnology include:

- **Bioanalysis tools: sensors, probes, arrays and microfluids.** These tools probe the surface of molecules and may be used in the analysis of genetic material and for diagnostic imaging. For example, nanoscale microarrays and microarray components are being developed for high-throughput screening applications. These have the potential to replace conventional microarray technologies, or be used in conjunction with them, to improve the sensitivity, precision and range of gene expression analysis (Mazzola, 2003). A variety of bioanalysis tools have been developed at the nanoscale for molecular labelling and tagging of, for example, proteins, amino acids and peptides. These are superior to existing technologies in terms of the range of labels available and the durability of the signal.

- **Diagnostic applications** include, for example, the use of nanodots to identify cancer-causing antigens and other pathogens. These have far greater sensitivity than existing tests, allowing for much earlier and more precise diagnosis of immune disorders. They may also enable clinicians to quantify, measure and track disease-causing agents (e.g. tumour cells) with far greater precision

than using current technologies. For instance, a new nanodot technology consisting of gold particles can be used to detect 10 or 20 molecules of prostate-specific antigen and is 10 000 times more sensitive than current tests (Vastag, 2004).

- **Therapeutic drug delivery mechanisms** are also being developed using nanotechnology. Nanoscale particles can be used to deliver conventional drugs to specific sites in the body. Existing drugs can be reformulated at the nano-scale and new drugs may eventually be designed at the nano-scale. This approach is particularly interesting in the treatment of cancer since it allows for much lower toxicity and greater effectiveness in the delivery of chemotherapies. Examples of nanodrugs used in oncology include BioScience's Abraxis which was approved by the US FDA (Food and Drug Administration) in 2005 for the treatment of metastatic breast cancer disease and Doxil for the treatment of ovarian cancer.

Early development and application of biomedical technologies often raise both the promise of significant benefits and concerns about unknown potential risks. The emerging area of bio-nanotechnology finds itself in the same position, an issue addressed below.

Anticipating and mitigating unintended consequences

The challenges presented by risk governance in nanotechnology are not dissimilar to earlier technologies, such as genetically modification of foods and the generation of nuclear power. Due to its distinctive interdisciplinary and pervasive nature, nanotechnology may, however, present a very unique need for integrated governance to anticipate and mitigate unintended consequences.

This has been recognised by, *inter alia*, the International Risk Governance Council (IRGC), an independent international organisation that studies global emerging risks. In 2005, the IRGC developed a risk governance framework[6] that intended to move beyond conventional risk management by formally advocating participation in policy-making of a broad range of relevant actors (scientific communities, industry, major stakeholders, society, etc.).

The framework responded to the need for change in the governance strategies being used for risks having international and pervasive implications and for technologies (and other) having the potential to harm human health and safety, the economy, the environment and/or the fabric of society at large. It aimed to strengthen the relationship between evidence and policy through the incorporation of a societal context and by using a new categorisation of risk-related knowledge. Within the framework, the concept of risk governance includes not only traditional risk analysis and risk management approaches, but also looks at how risk-related decision-making unfolds when a range of actors is involved, requiring co-ordination and possible reconciliation between a profusion of roles, perspectives, goals and activities, a theme continued below.

Closer co-operation and streamlined regulatory pathways

Bio-nanotechnology is generating a range of new products that are blurring the traditional boundaries between therapeutics and medical devices. This poses unique challenges for any regulatory agency because of the traditionally different timelines and development cycles and the multiplicity of configurations of the two categories of products. Integrated regulatory frameworks and closer cross-agency collaboration on policies and decision-making are needed to develop and apply these new technologies in a responsible way.

An illustrative example is the convergent nanotherapeutic product based on gold nanoshells developed by the United States' company, Nanospectra Bioscience. These nanoshells are essentially

nanosized particles of silica, coated in gold nanoparticles, which, when injected into the blood stream, naturally congregate at tumour sites. The nanoshell then acts as a lens, focusing infra-red light and capturing it around itself, thereby allowing tumours to be detected and imaged. Having served its diagnostic function, the gold nanoshell may also be used to destroy the tumour. An infra-red laser can be shone on the tumour site where the nanoshells have accumulated resulting in a temperature rise in the area around the nanoshells. The tumour is destroyed by the heat. The effect is similar to that of an implantable radioactive source, which is placed within tumours in order to destroy them. Thus, gold nanoshells have two distinct modes of action, both of which could be classified either as medicines and devices.

In the United States, the US FDA explicitly recognises combination products. It assigns regulatory jurisdiction based on the mode of action that is expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. In the case of the above example, given that the destruction of tumours is likely to make the greatest contribution to the overall intended therapeutic effect of gold nanoshells, application of the FDA definition would most likely result in them being regulated in the United States as medical devices. However, the risks associated with free nanoparticles *in vivo* may perhaps result in a call for the application of the more comprehensive safety and efficacy evaluation associated with the approval of prescription medicines.

In Australia, the Therapeutic Good Administration (TGA) has also recognised recently that some therapeutic products do not fit neatly within either definition and it provides a list of device/medicine boundary products that have been approved and identifies whether they have been classified as a medicine or a device. The list provides little assistance, however, in determining the most appropriate regulatory pathway for these new therapeutic products. The two distinct modes of action of gold nanoshells have been recognised by the TGA as both medicine and devices.

Progress in bio-nanotechnologies, and more broadly, in convergent biomedical technologies will require a reshaping of existing institutional structures to allow effective and timely regulatory review that cuts across traditional disciplinary boundaries. This is also true of the technologies considered in the next section, stem-cell derived therapies.

Biomedical and health innovation through stem cell-derived therapies

Scientific developments in the field of stem cell research continue to emerge at incredible speed. The promises and hopes are substantial: human stem cell research may lead to new methods of drug discovery, insights into mechanisms of disease and cellular therapies for regenerative medicine to treat conditions like Alzheimer's disease, diabetes, heart disease, osteoarthritis, osteoporosis, spinal cord injury, muscular-skeletal injuries and rare diseases that affect the normal functioning of the human body.

Stem cells are defined as cells that can self-renew and that can differentiate into specialised cells of the body. There are several types of stem cells including Adult Stem Cells and Pluripotent Stem Cells:

- Adult (or Somatic) Stem Cells (ASCs) are undifferentiated cells isolated from a specific organ or tissue from an animal. They are normally present to maintain and repair injured tissue or organs. ASCs relate to a specific tissue, are capable of generating only a few cell types of a given tissue and have a limited number of proliferation cycles. ASCs are present in tissues such as brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium and testes. Adult Stem Cells (e.g. hematopoietic stem cells, basal keratinocytes, stromal stem cells and foetal neuroblasts) have demonstrated their therapeutic value for over 30 years (e.g. marrow grafts and skin grafts for burn victims) (Goldring, 2011).

- Pluripotent Stem Cells (PSCs) are capable of proliferating indefinitely and giving rise to all cell types of the body and are also called "immortal" stem cells. They are either embryonic stem cells (ESCs), from an early-stage embryo, or induced pluripotent stem cells (iPSCs), artificially derived, typically from an adult somatic cell, through the induced expression of specific genes. Pluripotent stem cells have been successfully differentiated into numerous types of cells (e.g. cardiomyocytes, neurons, pancreatic beta cells, keratinocytes and melanocytes).

Despite the tremendous scientific and technical advances in the field (e.g. cardiac tissue repair; use of somatic cell nuclear transfer to create embryonic stem cells; creation of induced pluripotent stem cells from human skin cells and direct reprogramming of adult cells), the ethical and social debate has somewhat overshadowed the many other important issues that affect the stem cell field globally. These include: diverging and inconsistent national regulations and standards for the retrieval, storage, supply, trade and use of stem cells (Caulfield 2009 et al.; Wainwright et al., 2006); financing (Moran, 2007); and intellectual property issues (Spalding and Simkin 2007).

The stem cell policy landscape

As with other areas in biomedicine, stem cell research operates in a complex, international environment. In most OECD countries, the vast majority of stem cell research takes place in university research centres, hospitals and laboratories, although the private sector is also gradually becoming active in this field. Multiple institutional actors and stakeholders are involved in the translation of stem cell research from the bench to the bedside. Many of these have their own governance structures, often with diverging and, even competing, objectives, making their inter-relationships complex. This situation is further complicated by the diverging approaches that countries worldwide have adopted to regulate the area of stem cell research. The international stem cell policy environment has recently been described as a "patchwork of patchworks" (Caulfield et al., 2009).

Frameworks for stem cell research, and its application, range from constitutional and legislative to administrative approaches. They differ in degree from liberal to intermediate to restrictive (Isasi and Knoppers, 2009, Caulfield et al., 2009). At one end of the policy spectrum (restrictive) are countries that prohibit embryo research in general and, therefore, prohibit the derivation of stem cells from any source. A controversial compromise approach found within this restrictive policy framework is to allow for the use of imported stem cells while banning any further derivation and use. Other jurisdictions have opted for an intermediate position, permitting the use of excess IVF[7] embryos for stem cell derivation and research use, although in some circumstances additional restrictions may be in place. For example, these may limit the type (e.g. cryo-preserved or fresh) and range of uses of IVF embryos or ban stem cell derivation and use from other sources (e.g. human-animal combinations). Finally, at the other end of the spectrum, more liberal approaches allow a wider range of technologies to be used in stem cell derivation and research.

The requirement to demonstrate the provenance of the stem cells as a condition for obtaining a license is perhaps the single procedural mechanism with the greatest system-wide impact. Such oversight puts limits around and can even curtail access to stem cells and can therefore influence how research is conducted. Researchers have frequently dealt with these limitations by resorting to *ad-hoc* agreements. However, their actions provide only limited or temporary solutions and may be inconsistently applied, possibly even subjecting their users to some form of liability.

International governance of stem cell research through standardisation

The range of options for sourcing stem cells raises technical questions about the standardisation of stem cell science that could complicate the development of stem cell-derived therapies, particularly when it comes to tissue-based therapies (Loring and Rao, 2006) (Table 2). So far, standardisation in this field has

largely emerged through the self-regulating mechanisms of scientific practice: however, more rigorous standards and protocols are needed. Standards are important for product development, regulation, storage and traceability. The introduction of minimum standards, agreed internationally, could lead to safer and more effective treatment of patients.

Table 2. Potential sources of variation among human embryonic stem cell lines

Differences due to origin of cell lines	Genomic diversity Stage of blastocyst at derivation Conditions of early culture (feeder layer, culture conditions) Imprinting and X-inactivation
Differences arising over time in culture	Genetic changes (loss or gain of specific sequences) General and specific epigenetic changes (DNA methylation, histone acetylation) Differences due to mosaicism in cultures Partial or terminal differentiation of subpopulations within cultures Variation among epigenetic and genetic changes

Source: Loring and Rao (2006).Establishing standards for the characterization of human embryonic stem cell lines, *Stem Cells* 24, 145-150.

Since 2003, the International Stem Cell Forum (ISCF),[8] a consortium of 14 leading funders of stem cell research from around the world, has sought to address the topic of standards through an ambitious project "to carry out a comparative study of a large and diverse set of stem cell lines derived and maintained in different laboratories worldwide". The project was established under the governance of the ISCF along a hub-and-spoke principle, all work with the different cell lines being conducted by participating laboratories according to standard protocols provided by the consortium.

The ISCF also oversees the International Stem Cell Banking Initiative (ISCBI) – which aims to create a global network of stem cell banks, both by encouraging the setting up of new banks in member countries and by supporting existing banks. In addition, ISCF is currently acting as the governing body of several working groups addressing key issues for stem cell scientists and funders. These include two groups reviewing the ethical policies of countries throughout the world regarding stem cell research and the regulations for intellectual property rights in countries active in stem cell research.

The future of stem cell therapy may depend on the successful implementation of broad-based international collaborative mechanisms to achieve standardisation of practices, formalisation of networks ensuring quality of sources, enforcement of standards, and resolution of possible issues related to patenting and licensing of enabling technologies.

In a related activity, a central archive reference stock of key hybridomas (the cells that produce monoclonal antibodies) has been established by the UK Stem Cell Bank,[9] and samples of antibodies can be provided to participating laboratories for studies of antigen expression. In turn, the individual laboratories provide samples of RNA and DNA from their cells, which are analysed centrally for expression of specific genes and for imprinting patterns.[10]

The emergence of national stem cell banks is accompanied by the establishment of international initiatives addressing harmonisation and standardisation processes for stem cell research and banking. Examples of these initiatives are: the International Stem Cell Banking Initiative (ISCBI) mentioned above; the European Commission's Human Embryonic Stem Cell Registry (hESCReg); UMASS[11] International Stem Cell Registry; and the Registry of Human Embryonic Stem Cell Lines Provenance of the International Society for Stem Cell Research (ISSCR). Numerous biobanking and other clinical information initiatives are emerging in OECD and non-OECD countries (see Box 4).

In one such initiative, the United Kingdom recently announced an ambitious plan to fully sequence the genomes of 100 000 patients with cancer and rare diseases. This will require collaboration between biobanks across Europe and worldwide. In March 2012, the United Kingdom also opened the UK biobank,[12] which includes health information and blood samples of 500 000 people.

These initiatives share a common goal: the promotion of international collaboration for the timely realisation of the scientific promise offered by stem cell research. They seek to achieve policy harmonisation in conjunction with the harmonisation of technical standards and safety requirements. They further aim to provide guidance on how to navigate the "policy patchwork" (mentioned above) that characterises the current state of stem cell research (Isasi and Knoppers, 2009).

Box 4. Human biobanks and genetic research database initiatives across selected OECD countries

Human biobanks and genetic research databases (HBGRDs)[13], can serve as resources for storing and searching libraries of genetic and cell material and other clinical information. This will require linking biological and clinical information and the various data sources will need to be inter-operable. As the data will most likely be owned by multiple groups, new mechanisms may be needed to facilitate the sharing of data, information and research results (OECD, 2009a).

So far, the extent of the actual activities and the impact of networking and harmonisation have not been fully assessed (European Commission, 2010). With this aim, the Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre, in collaboration with the European Science and Technology Observatory (ESTO), undertook a study to: 1) obtain knowledge on the extent of biobanking in Europe and worldwide; and 2) analyse the relevant options and challenges for networking and harmonisation of biobanks. The conclusion of the work was that there is a real need to improve collaboration and networking among the numerous existing biobanks, as well as new emerging initiatives worldwide. Some examples of biobanking initiatives are presented in Table 3.

Source: Modified from European Commission (2010), Biobanks in Europe: Prospects for Harmonisation and Networking, JRC Scientific and Technical Reports, Spain; www.number10.gov.uk/news/dna-tests-to-fight-cancer/

Table 3. Examples of biobanking initiatives across selected OECD countries

Examples of biobanking initiatives by country	
Canada	PROCURE Quebec Prostate Cancer; Cancer Research Network of the FRSQ; Alberta Tumour Bank; Ontario Cancer Research Network; The Brain Tumour Tissue Bank; Capital Health/Regional Tissue Bank; CARTaGENE; Canadian Biosample Repository; Manitoba Breast Tumour Bank
France	Genethon DNA and Cell Bank; Biobanque de Picardie; Biological Resources Centres; Tumour Bank of Provence; Southwest France Tumour Bank
Germany	Central Biomaterial Bank; German Heart Failure Network; Patient DNA collection at Institute of Human Genetics Heidelberg; Danubian Biobank Consortium Tissue Bank; Charité-Universitätsmedizin Berlin
Japan	Health Science Research Resources Bank/Japan Health Science Foundation; Biobank Japan-Riken Institute; Japanese Collection of Research Bioresources; Japan National Cancer Center; Brain Bank for Aging Research
United Kingdom	UK DNA Banking Network; UK Stem Cell Bank; NHS Cod Blood Bank; Liverpool Tissue Bank; Confedeation of Cancer Biobanks; King's College Inectious Diseases Biobank; UK bBiobank Roslin Wellcome Trust Tick Cell Biobank

The safety challenge of stem-cell based therapies

Stem cell-based therapies bring with them safety challenges. To minimise the risk to patients, each stage of cell therapy production needs to be assessed for potential safety concerns, including the manufacturing process and the characterisation and formal safety assessment of the finished product. A major concern with stem-cell based therapies is their tumorigenic potential, which results from their unlimited potential for renewal and their capacity to differentiate into any human cell type. This is probably the most significant safety question at the current time and is not associated with any other type of treatment. Current monitoring techniques do not allow for the quantification of the tumour risk associated with the introduction of stem cells and stem cell-derived products in humans. Pre-clinical studies are conducted on mice with compromised immune systems, and it is unknown how this model might compare to a real patient and how the condition of the patient (age, disease, nutrition, gender, medication, etc.) might affect the efficacy of the introduced cells (Goldringet al., 2011).

Given the safety challenges associated with this new era of stem-cell based therapies, early and continuing dialogue between regulators, innovators and users can help to identify potential issues and to achieve the appropriate level of regulation. To address the issue of the regulation of stem-cell based therapies, the European Medicines Agency (EMA) created the Committee for Advanced Therapies (CAT) in 2008. The CAT is a multidisciplinary committee of regulators, academics, clinicians, companies and patient groups, whose objectives are to regulate new therapies such as stem-cell based therapies, also now referred to as Advanced-Therapy Medicinal Products (ATMPs). All new therapies are authorised centrally within the European Union, but the decision as to whether a country permits the use of the therapy is taken at a national level (e.g. in Germany, treatment with medicinal products containing embryonic stem cells is not permitted).[14]

In this sense, collaborative efforts between academia and industry may present an opportunity to define safety and efficacy biomarkers for stem-cell based therapies or as platforms to access data on pre-clinical studies, among others.

Concluding remarks

The three technology-based examples detailed in the above section highlight some of the main challenges policy makers are facing in the governance of biomedicine and health technology in the process of moving biomedical innovation and health technologies to point of care. This process entails several complex steps - from R&D to preclinical and clinical research to market authorisation - that involve multiple stakeholders from different communities: researchers, companies, regulators, economists, social scientists, ethicists, etc. Decisions have to be made in an environment of uncertainty about the impacts that new health technologies and biomedical innovation will have when made accessible to the patient. Evaluation of the ratio of risk to benefit – risk including risk for the patients but also potential risk to society – remains a difficult exercise.

Policy makers and regulators, but also companies and the research community, are very conscious of these difficulties and have tried to overcome them through the implementation of a number of initiatives and programmes, at national and global levels. Such programmes, examples of which are presented in Section II, are focusing in particular on modernising regulatory science and streamlining the governance of clinical research. The approval process for new medical products to arrive on the market raises its own particular set of issues that will be addressed in Section III of this report.

SECTION II: STREAMLINING GOVERNANCE FOR BETTER TRANSLATIONAL RESEARCH[15]

The previous section identified, though various examples, some of the main issues associated with the governance of biomedicine and health technologies, as also seen in previous work by the OECD.[16] Creating the conditions for the implementation of innovative diagnostics and therapies at point of care – through clinical and translational research – appears to be one of the greatest challenges, involving multiple stakeholders from various communities, interacting in an environment of uncertainty. That uncertainty creates problems for decision makers because they are charged with choosing between various options while there is insufficient definitive information on which to base decisions.

This section considers specific initiatives that have been set up to remove barriers and streamline the flow of innovation from the laboratory bench to the bedside, such as modernising regulatory science and improving the governance of clinical trials while maintaining effective safeguards.

Streamlining governance of clinical trials

A priority area for all OECD countries is that of streamlining the governance of clinical trials, particularly that for early-stage trials. This can be achieved by speeding up the initiation of trials, undertaking early proof-of-concept studies and improving patient recruitment. Countries are seeking to improve the development of clinical trials at national level but also, as clinical research increasingly becomes global, to assure harmonised practice in clinical trials internationally (see Box 5).

Regulatory bodies are structured around the monitoring of the quality of clinical trial data and the safety of drugs and devices in their domestic markets. They have limited information on many aspects of the research conducted outside of their jurisdictions or countries, including information on the sites used, the investigators involved, the methods used for selection of participants and the quality of trial data. Hence, the need to re-assess and strengthen the international clinical trial paradigm has never been greater.

Box 5. Improving clinical trials

Today, regulators in OECD and non-OECD countries alike are systematically assessing frameworks for the oversight of clinical research. The following are some examples:

- Evaluating current regulatory frameworks is a key objective under the Health Canada initiative "Blueprint for Renewal".[1]
- In Europe, the Road Map Initiative for Clinical Research brings together representatives of academic and not-for-profit organisations to investigate possible improvements to the European Clinical Trials Directive (DIR 2001/20/EC).
- In Singapore, the Health Sciences Authority has launched a comprehensive effort to bring products to the healthcare market more quickly and cost effectively by leveraging Singapore's relationships with regulatory authorities in other countries and by the innovative use of scientific data.
- In the United States, the FDA is collaborating with the National Institutes of Health (NIH)[17] with respect to two inter-related scientific disciplines: translational science, the shaping of basic scientific discoveries into treatments; and regulatory science. As part of the effort, the two agencies have established a Joint Leadership Council to spearhead collaborative work on important public health issues. (See also Box 6)
- In Germany, the Ministries of Health, Education and Research, as well as those for Economics and Technology have been working in conjunction with the responsible authorities, representatives of industry, and statutory health insurance funds in order to improve framework conditions for regenerative medicine and to make stem cell therapies available to patients more quickly and at affordable prices.[18]

There are also a growing number of international and regional collaborations (e.g. in the European Union and APEC area). Regulators from different countries meet regularly through the International Conference on Harmonization on topics as diverse as confidentiality agreements, advanced therapy medicinal products and the exchange of pharmaco-vigilance information. In 2009 the FDA and the European Medicines Agency[19] agreed to a bilateral Good Clinical Practice initiative to help ensure that clinical trials are conducted uniformly and ethically in Europe and the United States.

Note: 1 See more information on the Health Canada website at, www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/index-eng.php

Below are examples of approaches to improve clinical trials at national and international levels.

The OECD Recommendation on the Governance of Clinical Trials

Tight national regulations have been introduced over time to ensure the quality of clinical trials and, thereby, the safety of patients. Depending on the country and on the nature of the trial, supervision is either based on specific legislation, or on rules originating from the competent authorities, or on ethical guidelines alone. As a result, the regulatory mechanisms that are applicable differ widely across countries. The current administrative complexity is such that it leads to many well-conceived clinical trials aimed at addressing important public health problems either not being conducted or to being so delayed that their impact is dramatically reduced.

An OECD Council Recommendation on the governance of clinical trials was issued recently (OECD, 2013). This recommendation aims to facilitate international co-operation in clinical trials of medicinal products, particularly trials initiated by academic institutions. Its primary focus is on improving the consistency of national regulations and their interpretations, and on streamlining procedures for the oversight and management of clinical trials, by introducing a proportionate regulatory approach, while also enhancing the protection of trial participants.

The Road Map Initiative for Clinical Research in Europe

The Road Map Initiative for Clinical Research in Europe brings together representatives of academic and not-for-profit organisations who have been involved in an EU-funded project to investigate different aspects of the clinical trials environment in Europe, following the implementation of the European Clinical Trials Directive (DIR 2001/20/EC), and to promote academic clinical trials. The main goal of the Road Map Initiative is to propose improvements to the legislation thereby facilitating the performance of clinical research, for the benefit of patients, and increasing the competitiveness of clinical research at the European level.

The European Clinical Trials Directive was adopted in 2001 to harmonise the EU regulatory environment for clinical research. It aimed to improve the protection of participants, optimise the use of safety information and ensure the validity of data, through increased responsibility of the sponsors and through harmonised trial authorisation procedures across European member states. The risk profiles of research protocols, however, may still vary considerably depending, for example, on factors including:

- The extent of prior knowledge about the disease and the product being investigated;
- The population of patients involved;
- Whether the medicine is being assessed for approved indications or other therapeutic uses.

In July 2012, the European Commission adopted a "Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use", repealing Directive 2001/20/EC.[20]

The Proposal identifies areas for change as follows:

1. Adoption of a risk-based approach: adaptation of the regulatory requirements considering the risk associated with the trial with regard to the safety reporting (e.g. limited safety reporting for commercially approved drugs), data monitoring, insurance, application dossiers, substantial amendments, free-of-charge supply of drugs (not in the case of market approval);
2. Simplification and harmonisation of the procedures for clinical trial approval and safety reporting (for example, requiring only one Clinical Trials Authorisation (CTA);
3. Definition and harmonisation of the roles of the ethics committees (achieving a so-called "single opinion") and the competent authorities;
4. Co-sponsorship in the case of multinational trials, with the aim of facilitating collaboration between research groups;
5. Harmonisation of insurance requirements (i.e. uniform costs per country, minimum and maximum indemnity payments, total duration of coverage, time to permit claims, etc).

The proposal has been submitted to the European Parliament and the Council for processing.

Improving clinical trials in the United States

In 2005, the National Cancer Institute (NCI) established a Clinical Trials Working Group (CTWG), whose mandate is to recommend ways by which the national clinical trials enterprise could be restructured to realise the promise of molecular oncology in the 21st century. To meet this challenge, the CTWG first

reached consensus on four critical goals for designing a more efficient national system for clinical trials conducted or supported by NCI:

- improving co-ordination and co-operation among the functionally-diverse components of the system;
- improving prioritisation, based on robust evidence-based science and the needs of patients;
- improving standardisation of tools and procedures;
- improving operational efficiency.

These four goals make up a framework for 22 initiatives recommended by the CTWG and designed to support a powerful and transparent clinical trials enterprise, integrating the individually strong components of the current system into a cross-disciplinary, scientifically-driven, co-operative research effort.

In 2007, the FDA's Office of Critical Path Programmes announced a new public-private partnership aimed at improving the quality and efficiency of clinical trials. Under an agreement with the FDA, Duke University hosts a collaboration known as the Clinical Trials Transformation Initiative (CTTI). As founding partners, the FDA and Duke University enlisted diverse stakeholders in the clinical trials enterprise to participate in the initiative. Currently, over 50 organisations take part in CTTI, including government agencies (the FDA, Centres for Medicare and Medicaid Services, Office of Human Research Protections, NIH and other national and international governmental bodies), industry representatives (pharmaceutical, biotech, device and clinical research organisations), patient and consumer representatives, professional societies, researchers, academic institutions and other interested parties.

Clinical trial transformation initiatives in the United Kingdom

The National Health Services (NHS) and United Kingdom clinical research networks are seeking to develop standardised and harmonised procedures for ethical approval and new methods for conducting clinical trials in an explicit attempt to speed up the late-stage development process for new therapeutics.

The United Kingdom Clinical Research Network (UKCRN)[21] is a network of research staff working in the NHS. It provides a framework for clinical trials and other biomedical research studies funded by the public, charitable and industry sectors. The National Institute for Health Research (NIHR) Network Co-ordinating Centre is responsible for its co-ordination across the United Kingdom through centralised systems (e.g. for obtaining NHS permission for commercial and non-commercial clinical research studies) and by undertaking cross-cutting activities to support the commercial life-sciences industry, to develop the research workforce and to promote patient and public involvement in clinical trials. By 2008, 133 industry sponsored trials had been placed in the NIHR Clinical Research Networks. (IBP USA, 2011)

Redefining the way regulators interact with each other is just one part of the series of changes needed to support the goal of improving the clinical research environment. Building credible and efficient regulatory institutions also means addressing resource and capacity constraints.

Modernising regulatory science: encouraging early dialogue

There is evidence today that the decision-making process can be strengthened by early dialogue between regulators and the regulated, and also with other stakeholders including patient groups, clinicians, and the representative public, in the appraisal of new biomedical technologies. Early consultation is becoming indispensable in generating the necessary information for policy formulation. Innovators are

often more and better informed than regulators in relation to at least some kinds of technical and scientific developments, particularly in the case of biomedical innovations.

Increased transparency in the decision-making process and the open acknowledgment of ethical concerns and local values can also enhance the decision-making process and generate greater legitimacy in the eyes of the public. Important questions for decision makers are: *"Where and when should early dialogue be established and the full breadth of perspectives on new technology comes into play? What is the opportunity cost of not engaging in an early dialogue? How can the regulator and the regulated best work together?"*

Regulatory modernisation can involve changing the mix of instruments used, amending existing regulations, or rethinking the laws or Acts upon which regulations are based. The general aim of these initiatives is to respond to the new wave of emergent biomedical and health innovation technologies through consistent, risk-based approaches to regulation, keeping pace with what is known about the ethical, legal, scientific and social implications of these new technologies.

Recent experience in the United Kingdom has shown that there may be both opportunities and hazards to upstream engagement of the public. Early consultation can provide opportunities to inform the public. It may, however, also prematurely frame new technological developments in ways that are not representative of how these same technologies may ultimately be translated and used in clinical practice. Other national initiatives have emerged with similar goals (see Box 6).

Box 6. Example of regulatory modernisation initiatives

Canada: Health Canada's modernisation initiatives, such as the *Blueprint for Renewal,*[22] are focusing on modernising outdated regulations and tools for new product categories, building stronger compliance and enforcement capacity, and strengthening post-market surveillance systems. Health Canada has recently identified nine key areas for improvement. One of these areas is Risk-Based Regulatory Business Transformation (RBRBT) which, in turn, has three sub-streams of work: streamlining regulatory processes and horizontal decision making; strengthening risk-based regulatory policies; and improving engagement and communication. The new *Cabinet Directive on Streamlining Regulation,*[23] approved in 2007, reinforces the Blueprint's key principles and initiatives, by ensuring that regulations achieve their intended outcomes. The Directive also introduces two new requirements for more rigorous cost-benefit analysis and for demonstrating that every regulation has a net benefit for society. It marks a shift away from the previous narrow focus on regulatory development toward a broader approach that requires on-going consultation with affected parties throughout the regulatory cycle - from development of regulations through implementation, evaluation and review.

United States: The United States Food and Drug Administration (USFDA) announced in February 2010 a collaboration between the National Institutes of Health and the USFDA.[24] The initiative involves two inter-related scientific disciplines: translational science, the shaping of basic scientific discoveries into treatments; and regulatory science. In this context, the two agencies established a Joint Leadership Council for collaborative work on key public health issues. In addition, the National Institutes of Health (NIH) and the USFDA have jointly issued a Request for Applications, making USD 6.75 million dollars available over three years for work in regulatory science. The research supported through this initiative is meant to add to the scientific knowledge base by providing new methods, models or technologies that will inform the scientific and regulatory community about better approaches to evaluating safety and efficacy in medical product development.

Two major initiatives to support new platforms for co-operation that facilitate dialogue among stakeholders and help shorten the path for developing new medical products, are briefly described below:

The Critical Path Institute

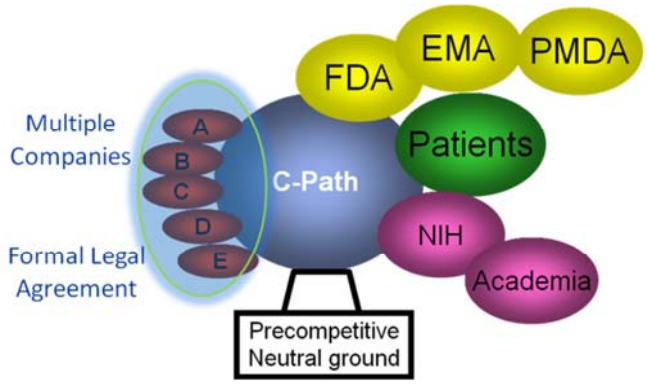
The Critical Path Institute (C-Path) is a public-private partnership. Created in 2005 by the University of Arizona and the US FDA, it is an independent not-for-profit institute, unaffiliated with any single entity or interest group. Its neutral status allows C-Path to serve as a facilitator for discussions between scientists from the government, academia and the private sector. To avoid any potential or perceived conflict of interest, C-Path does not accept funding from organisations that develop products regulated by the FDA (see Figure 1).

Key principles of how the C-Path Institute operates include:

- Allowing sponsors to come together in a pre-competitive space;
- The promotion of standard formats and clear and transparent rules of engagement;
- Reaching out to patients early on;
- Sharing information about both successes and failures.

In its five years of existence, C-Path has facilitated regulators engagement in scientific discussions with the "regulated" and cross-border collaboration on biomedical research through various consortia.

Figure 1. The Critical Path Institute's consortia model



Source: OECD based on the OECD Workshop on Better Health through Biomedicine: Innovating Governance, 27-28 September 2010, presentation from Martha A. Brumfield (Director of International Programs, Critical Path Institute)[25]

The Innovative Medicine Initiative

The Innovative Medicine Initiative (IMI) - a joint initiative of the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) is perhaps the largest public-private partnership in the world. Its overall goal is to build a more co-operative ecosystem for biomedical research in Europe. Created in 2007, the Innovative Medicines Initiative Joint Undertaking (IMI JU) of both the European community and industry, implements IMI and is responsible for the launch of Calls for

Proposals and the awarding of grants. The overall objective of the initiative is to encourage more rapid discovery and development of better medicines for patients while improving the prediction of safety (early indications of safety problems) and of efficacy (early indication of efficacy by use of biomarkers); to bridge knowledge management gaps (collaboration to break information barriers at the interfaces); and to bridge educational gaps (across pre-clinical and clinical research and between disciplines).

These initiatives represent promising and innovative ways to promote effective knowledge flows internationally. Creating consortia for pre-competitive knowledge can speed up the pace of innovation in early stage research, such as for biomarker validation, and perhaps avoid or reduce patent thickets or anti-commons which deter innovation. By sharing knowledge about failures, or know-how about regulatory procedures, development costs may also be reduced.

Concluding remarks

Improving the translational and clinical research environment involves:

- Advancing regulatory science on a global scale;
- Developing the foundations for common standards in evidence development and data sharing;
- Bringing main actors together at an early stage;
- Identifying new ways to share and manage knowledge;
- Incorporating patient values and interests in early stages of clinical research;
- Increasing collaboration between the private and public sectors.

These improvements all aim to facilitate the market approval process for new drugs or medical products more generally. Indeed, the market approval process carries particular risks as it is the definitive step in allowing an innovation to be available to the patient. The main issues associated with the governance of the market approval process are discussed in the next section.

SECTION III: GOVERNANCE OF THE MARKET APPROVAL PROCESS[26]

The challenge for health policy-makers is to develop and implement strategies to harness the benefits of technology and innovation while, at the same time, achieving multiple health-system objectives – all within national economic constraints.[27] Part of their role is to determine policies on the provision of diagnosis and treatment including ensuring that new drugs reach patients in a safe and timely manner, having passed through a rigorous market approval process.

Two main strategies for managing the approval process, and in particular for managing uncertainty around new and modified treatments, have been identified: first, creating closer links between the innovators and policy-makers; and, second, applying risk-sharing strategies, such as conditional market approval mechanisms. Uncertainty arises when decision-makers face a reduced ability to answer the following kinds of questions: *"Which individuals will benefit from the technology? By how much and for how long will they benefit? How much do these benefits differ from those provided by current standard treatments, and at what additional or reduced cost?"*.

This section covers governance issues associated with the approval process through which new medical products reach the market. It also describes some of the national and other initiatives and mechanisms that have been developed to overcome uncertainty in decision-making with respect to new medical products.

How much information is enough to allow a drug onto the market?

The key question is how much information is both necessary and sufficient for a new therapeutic product to be approved for release into the health system. Knowledge about the benefits and risks of a new biomedical product or therapy grows over time. Along this continuum of information gain, the regulatory approval threshold (i.e. the point at which enough information is available to enable regulators to decide whether or not a product should be released onto the market) can vary with time.

Indications are that this threshold may, to some extent, also depend on the degree of unmet medical need. For example, a life-threatening disease for which there is no effective treatment (high unmet medical need) would have a low relative need for information. In conditions of exceptionally high unmet medical need, regulators may temporarily lower the requirement for comprehensive benefit/risk data ("knowledge"), to enable rapid access to promising drugs.

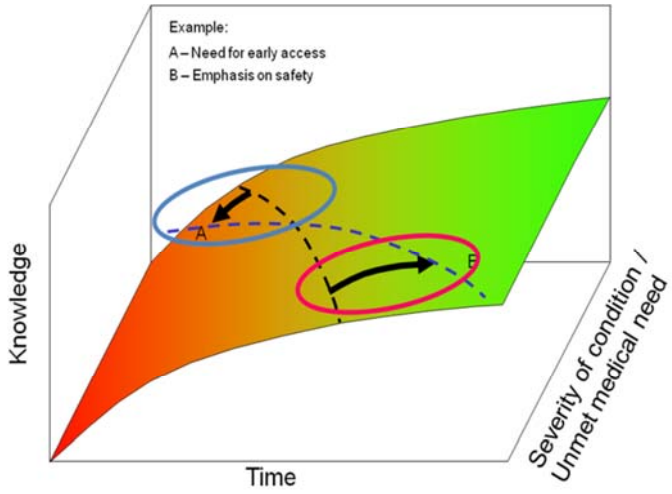
In Figure 2, the link between medical need and information need is depicted by the black line running diagonally across the "knowledge surface". The arrows indicate possible scenarios in the current debate on regulatory practice and the trade-offs between early access and the need for sufficient information on benefit/risk assessment. The scenario mentioned above, where high unmet need is addressed by a lowering of the data barrier, is depicted in A - the threshold moves temporarily to the left.

In contrast, for some drug classes that do not address life-threatening diseases, an emerging safety issue may bring about requirements for additional pre-marketing clinical studies of such a size or duration as to render the approval of such products unrealistic without more knowledge being available - the regulatory threshold moves to the far right as depicted in B.

There has therefore been gradual divergence over time in the regulatory requirements for the approval of drugs for life-threatening versus non-life-threatening diseases.

Without input from patients, however, product development misses out on valuable insights into their needs and wants e.g. what risk patients are prepared to take during a course of treatment. The pressure that is put on healthcare systems in dealing with medically-sound but expensive innovations, and the resulting challenges for fair allocation of treatment in society, may be helped by greater involvement of patients in the decision-making process.

Figure 2. Evolution of the regulatory threshold



Source: OECD based on the OECD Workshop on Better Health through Biomedicine: Innovating Governance, 27-28 September 2010, presentation from Hans-Georg Eichler (Senior Medical Officer, EMEA, United Kingdom)[28]

From an "all or nothing" position to life-cycle management

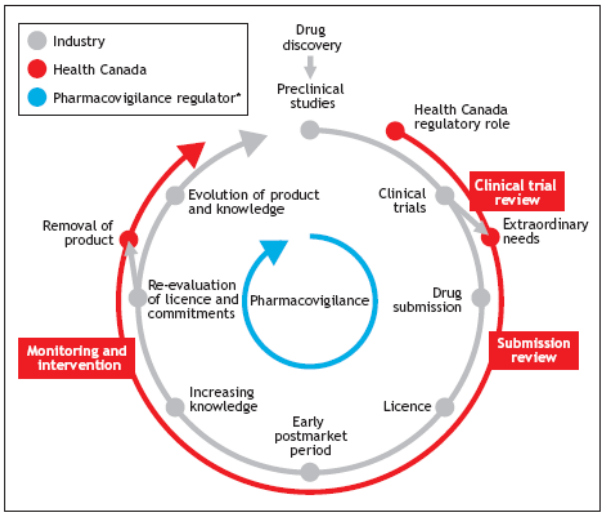
There is broad agreement among regulators and within the scientific community that the point of approval (or rejection) should not be the "last call" for major regulatory action but that risk/benefit assessment should be an ongoing activity, ideally spanning the full life-cycle of a product. To achieve this goal, various countries have enacted, or are considering, legislation and/or regulations to establish risk-management systems (RMS). One example is the recent European legislation that provides for mandatory RMS, defined as: "a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions". Applicants requesting market approval for a therapy are asked to submit a detailed risk-management plan (RMP), for example, as part of the marketing authorisation application dossier or on a number of other occasions specified in the legislation.

Essentially this means moving from an "all or nothing" position (to either license the drug or not) to an approach that allows drugs to be followed and assessed throughout their entire life-cycle.

In Canada, the progressive licensing framework is being developed under this assumption, that knowledge and experience about a therapeutic product can be gained at every stage of its life cycle (Figure 3). The framework aims to ensure that continuous re-evaluation of the risks and benefits of medications will identify any serious safety issues earlier and will improve the targeting of drug therapy through a move from passive pharmaco-vigilance to proactive risk management. This life-cycle approach also aims to enable the relevant authority (currently Health Canada) to:

- Better serve patients, consumers and healthcare professionals by supporting them in making informed decisions based on the best possible information available;
- Support early identification of risks, and implementation of successful risk management activities;
- Create more opportunities for professionals, patients and consumers to be involved in decision-making regarding therapeutic products;
- Better address a wide range of needs, including those of patients with rare diseases.

Figure 3. Canada's Progressive Licensing Framework



Source: OECD based on the Health Canada website, see: www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php, accessed June 2013

All regulatory decisions are taken under conditions of uncertainty. Even when efficacy of a medicinal product is assessed under controlled experimental conditions, uncertainty arises from multiple sources, such as gross experimental error, systematic error and bias, and random error. Random error, characterised as the well-known type I and type II errors of clinical trials (that is, the risk of reaching a false positive or false negative conclusion, respectively), can be limited but not eliminated. In addition, at the time of product review, the following information may be incomplete or missing:

- Information on population safety issues;
- Information on drug interactions;
- Information in full target population for the marketed product;
- Information comparing to existing drugs;
- Information on appropriate utilisation;
- Information on long term use.

As a reaction to this uncertainty and recent high profile drug withdrawals from the market (for example, androfecoxib (Vioxx)), the regulatory process in many countries has become highly conservative about what can be approved and reimbursed. Borrowing from the terminology used in statistics, regulators are generally leaning towards the Type II error – i.e. false negative conclusion - denying access to a therapeutic product that may ultimately prove beneficial.

Inevitably, this has consequences for entrepreneurship, investment and innovation. It may have a significant impact on access to new and more effective drugs and the choices available to patients.

Creating conditions for patient access through conditional coverage

Although new drugs may offer health benefits, their high prices raise questions of affordability, and concerns about the relative health benefits per unit price. These concerns reflect the broader challenge of assuring value for money in healthcare and achieving best allocation of resources. One way to enhance patient access, while keeping costs down, is by redistributing the risk balance between purchasers and manufacturers.

The use of risk-sharing agreements, in the form of conditional approval mechanisms, is yet to be fully evaluated, but it may offer some prospect of better and more rapid integration of new biomedicine and health innovation technologies into clinical care. The United Kingdom has been at the forefront of developments in Europe by introducing, since 2002, schemes including (Table 4):

- Risk Sharing or outcomes-based coverage (the manufacturer agrees to reimburse drug costs if certain long-term endpoints are not met);
- Response Rebate (the manufacturer agrees to reimburse drug costs in non-responders);
- Cost capping/discount (the manufacturer agrees to provide product at a lower price than listed);
- Dose capping (the manufacturer agrees to provide a free product after a certain number of doses); and
- Free 1st cycle (the manufacturer provides the first dose for free).

Risk-sharing (or value-based) agreements have a pre-specified endpoint or a definition of response that dictates if the purchaser will cover the treatment. The contracts are based on the concept that the innovator will only be paid if the product provides value to the patient, thereby redistributing the risk associated with the use of any previously untried products. A problem with this type of scheme is that there may be significant uncertainty about the history of the disease to be treated; therefore patient outcomes may not be easy to monitor and evaluate.

Table 4. Examples of patient access schemes

Date	Product	Indication	Type
01/02	Beta-interferon	Multiple sclerosis	Risk sharing
10/07	Bortezomib	Myeloma	Response rebate
07/08	Drug eluting stents	Angina	Cost capping
08/08	Ranibizumab	Macular degeneration	Dose capping
11/08	Erlotinib	Non-small-cell lung cancer	Cost capping
03/09	Sunitinib	Renal carcinoma	Free 1st cycle
06/09	Lenalidomide	Myeloma	Dose capping
08/09	Cetuximab	Colorectal cancer (first line)	Discount
09/09	Sunitinib	GIST	Free 1st cycle
09/09	Ustekinumab	Psoriasis	Cost capping
12/09	Trabectin	Soft tissue sarcoma	Cost capping
02/10	Certolizumab	Rheumatoid arthritis	Free 1st cycle
07/10	Gefitinib	Non-small-cell lung cancer	Cost capping

Source: OECD based on the OECD Workshop on Better Health through Biomedicine: Innovating Governance, 27-28 September 2010, presentation from Michael Rawlins (Chairman of the National Institute of Health & Clinical Excellence (NICE), United Kingdom)[29]

Decision on coverage is often based on two determining factors: 1) the test has proven its validity and utility in clinical care; and 2) its value to the health system (typically based on comparative cost-effectiveness). Reliance on positive health outcomes is often a primary factor in deciding coverage. Although randomised clinical trials (RCTs) have proved technically and economically feasible for drugs and biologics, and are considered to be the gold standard for producing scientific evidence on the risk/benefit profile of therapeutic interventions, the practical implications of broadly applying the same standards to new biomedical therapies, devices, diagnostics, and procedures can be challenging, for example in the case of rare diseases with a small number of patients (as mentioned before).

One example is the pharmacogenetic-based dosing of Warfarin. Evidence of the clinical utility of Warfarin was obtained through a large-scale cohort study by Medco, a US-based company that provides pharmacy benefit management services for nearly one in five US Americans. The study, which relied upon Medco's integrated system of medical and pharmacy claims, indicated that hospitalisation rates for heart patients taking Warfarin fell by almost one-third when genetic information was available to assist doctors in prescribing the drug. Equally important, the study considered factors not usually addressed in RCTs but of significance in translating a product into clinical practice, namely, the attitudes of patient and physicians to pharmacogenetic testing (PGx) and the willingness of purchasers to reimburse for the test (See Box 7).

Box 7. Dosing Warfarin: To test or not to test?

Pharmacogenetic-based dosing of Warfarin is a frequently-cited example of personalised medicine. Warfarin is used to reduce the risk of death, heart attack or stroke after a patient has had a heart attack. It is also used to treat and prevent venous thrombosis (blood clots) and pulmonary embolism associated with atrial fibrillation or heart valve replacement surgery. Warfarin therapy requires regular patient monitoring because of its narrow therapeutic range, meaning that the dose needed to obtain a therapeutic effect is very close to the dose that can cause serious adverse events.

Studies evaluating the connection between genetic profiles and Warfarin use have shown that the doses people are eventually stabilised on are related to genetic profiles. Polymorphisms in the VKORC1 gene account for 30% of the dosing variability, and variations in the CYP2C9 gene explain 10% of dose differences between patients. Less well established, however, is the relationship between genetic profiles and outcomes of Warfarin use such as clotting and bleeding. So far, several high-profile RCTs have sought to determine whether genetic testing to inform dosing of Warfarin is clinically useful but these studies have yielded mixed answers.

In August 2007, the United States Food and Drug Administration revised the labelling for Warfarin, suggesting that clinicians should consider genetic testing before administration of the drug. However, the data on clinical efficacy was deemed insufficient for reimbursement purposes for such testing. The Centres for Medicare and Medicaid Services (CMS) in the United States announced in early May 2009 that genetic tests to help guide Warfarin dosing for Medicare recipients would not be paid, noting that the "available evidence does not demonstrate that pharmacogenomic testing to predict Warfarin responsiveness improves health outcomes in Medicare beneficiaries."

CMS did, however, leave open an option for coverage to beneficiaries who agreed to be part of a prospective, randomised, controlled clinical study designed to show that pharmacogenomics-guided dosing strategies improve health outcomes over standard dosing methods (under its Coverage with Evidence Development programme).

Source: OECD based on Epstein R.S. Moyer, TP, Aubert, RE, O'Kane DJ (2010), "Warfarin Genotyping Reduces Hospitalisation rates", American College of Cardiology, Vol. 55, pp. 2804.

Financial and outcome-based risk sharing agreements

Traditionally, those who pay take on most of the risks associated with purchasing new medical technologies. Risk-sharing initiatives seek to redistribute the risk between the purchaser and the technology or therapy suppliers. Risk-sharing arrangements for medical interventions typically arise for new, relatively high-price products, around which there is uncertainty as to the total patient outcome (e.g., a new cancer therapy effective in treating some cancers in some patients but not all cancers in all patients).

There are essentially two approaches to risk-sharing: finance-based and outcome-based. Finance-based schemes rely on a set of pre-specified budget caps, discounts or restrictions that can either relate to a particular patient or on the disease population. These can include price-volume agreements (as in France), expenditure caps (as in Australia and the United States), price cuts that are attached to forecast spend (Japan) and conditional discounts (as in Italy and the United Kingdom).

Outcome-based agreements are based on a pre-specified endpoint or the definition of a response that dictates whether the purchaser will cover the treatment on an ex-post basis. These can include outcome guarantees (as in the United Kingdom and the United States) and are a traditional model of risk-sharing agreement, as payment is weighted entirely against the performance of the drug. In essence, they are based on contracts that pay the innovator only in the event that the product provides value to the patient. These can be used to redistribute the risk associated with the use of such new products.

The United Kingdom has been at the forefront of developments in Europe. A frequently-cited example involves the compound bortezomib (Velcade) for the treatment of multiple myeloma. In 2006, the National Institute of Health and Clinical Excellence (NICE) rejected Velcade for reimbursement by the United Kingdom's National Health Service (NHS), to significant negative public reaction.[30] Velcade was not considered a cost-effective treatment option, at a price of c. USD 50 000 per quality-adjusted life year

(QALY) for the treatment of any first relapse and with the potential to reach over USD 160 000 for any subsequent relapse.

Following this decision, the manufacturer, Johnson & Johnson, decided in 2007 to negotiate a refund scheme that stated that if a patient achieved a complete or partial response (≥50% reduction in serum M-protein) within the first four cycles of treatment, the NHS would pay the full cost of therapy. Conversely, if a patient had a reduction of ≤50% or proved non-responsive, the company would reimburse the NHS the entire cost of treatment.

A similar strategy was adopted by Merck-Serono who agreed to reimburse primary-care trusts the cost of any vials of its metastatic colorectal cancer drug Erbitux (cetuximab) used by patients who failed to respond to therapy at six weeks. Another example was Pfizer who gained approval for its kidney cancer drug Sutent [sunitinib malate] in part by agreeing to offer the first cycle of treatment to NHS patients for free. Celgene entered into an agreement with the NHS regarding its multiple myeloma drug Revlimid (lenalidomide) in which the company agreed to pay all costs for patients who stay on the drug after 2 years (Barham, 2007).

In February 2007, the Office of Fair Trading (OFT) produced a critical study of the Pharmaceutical Price Regulation Scheme (PPRS) stating that, if the data at time of launch is insufficient to take an informed view of cost-effectiveness, then in a limited number of cases, such as for chronic conditions, a scheme should be adopted.

In the United States, United Healthcare agreed on a risk-sharing plan for Oncotype DX - a genomic biomarker assay that determines the likelihood of disease recurrence in women with early stage invasive breast cancer who are oestrogen-receptor positive (ER+) and whose lymph nodes test negative. The test might serve to screen some breast cancer patients away from chemotherapy by identifying them as patients unlikely to benefit from chemotherapy. Under the risk sharing agreement, if sufficient numbers of patients were not diverted from chemotherapy the insurer would seek a lower price. To ensure that the test was being used appropriately, United Healthcare entered into a risk-sharing scheme with the developer, agreeing to reimburse the test for 18 months, during which time both parties would monitor the results. If an excessive number of women with low risk scores were still receiving chemotherapy, United Healthcare would re-open the contract and negotiate a lower price. With this strategy, Oncotype Dx became the first clinical test to successfully command a high price based on comparative cost-effectiveness and value, USD 3 400 per test, as well as gaining reimbursement by most third-parties.

Agreement to reimburse only those patients that respond to treatment makes the response rebate scheme particularly attractive for payers. The down side of the scheme is that evaluation and monitoring of patients currently imposes a significant administrative burden. Today an established and effective infrastructure to manage these schemes does not exist. The introduction of electronic health records promises to greatly facilitate these efforts in the future.

The risk-sharing approach appears to be rapidly taking hold as it clearly offers potential benefits to all main stakeholders: purchasers and providers, manufacturers and patients. For the manufacturer, an agreement may open up market access for a product that may otherwise have been denied coverage on the grounds of expense, particularly in the case of uncertainty about its effectiveness. For purchasers, aside from the obvious opportunity to reduce the cost associated with the introduction of an expensive new product, the benefits are in risk-sharing for a product whose long-term prospects are uncertain. Patients are able to access potentially superior life-saving products more rapidly. Risk-sharing is, therefore, perceived by many as an additional strong incentive for companies to focus on identifying and validating clinically relevant biomarkers for existing and pipeline products.[31] Successful risk-sharing does, however, strictly

depend on agreeing and putting in place an appropriate methodology for monitoring and validating the effectiveness of a drug.

Concluding remarks

In summary, approaches to facilitate the decision-making process for market approval of new medical products appear to be spreading rapidly. They mark a paradigm shift, towards more value-based agreements. They offer potential benefits to all main stakeholders: purchasers and providers, manufacturers and patients. For the manufacturer, an agreement may open up market access for a product that may otherwise have been denied coverage on the grounds of uncertainty about its relative cost-effectiveness. For purchasers, there is the opportunity to reduce costs and to increase the number of potential useful treatments reaching patients. Finally, for patients, the benefit is in faster access to potentially life-saving products. The sustainability of these schemes - as well as the many related methodological, economic, and infrastructure issues - might be constructively explored through international exchange on good practice.

Despite increases in funding over the last decade, and in the face of great scientific and technological progress, it still remains the case that fewer products are making it to the market. Several sources indicate a decline in New Drug Applications (NDA) and the development time for new drugs remains long and the attrition rate remains high (Contonpoulos-Ioannidis, 2008, Peck, 2007).

CONCLUSIONS AND FUTURE WORK

Recent advances in biomedicine and health technologies represent significant opportunities to address unmet public health needs. However, innovation in these areas constantly challenges current governance frameworks, which need to adapt to novel types of medical products often directed at complex diseases. To efficiently translate biomedicine and health technologies from the laboratory bench to the bedside, governance frameworks are having to change to take into account the complexity of the field, using new (and often) iterative regulatory processes.

The report reviewed some of the collaborative and integrated approaches to governance and regulation that have gradually been emerging. Multi-stakeholder partnerships are gaining influence, encouraging the development of new norms of behaviour and evolving in diverse areas such as product licensing, standard setting and risk management.

These emerging initiatives aim to facilitate a more efficient translational research environment and reduce the time-to-market for regulated products, but some questions still remain: *"Can these initiatives be considered prototypes of tomorrow's mainstream approaches to governance, or are they transitory local attempts to identify more efficient policy approaches, governance and institutional design? What is government's role in shaping these developments to make the most of new biomedical discoveries for both individuals and society?"*

Some insights arise from the issues discussed in the report:

- **The importance of collaborative structures.** While the value of collaborative structures (e.g. between manufacturers, purchasers, regulators and patients) has been illustrated here through various examples, such structures must be fit for their particular purpose and lead to the most appropriate collaboration. The mechanisms and processes described in this report may be a result of a specific need coming from the geographic location, political or disease reasons (endemic pathologies, access to different patients). Further work will be required to tease apart the governance elements of successful collaborative mechanisms. Another area for further development is that of the generation and use of the data arising from collaborative initiatives, as well as the ownership of personal data; and the standards for sharing data. Better management and integration of scientific data and technological advances will remain a challenge for scientists and regulators until new models for creating, sharing, analysing and managing data are developed.

- **Developing early dialogue with stakeholders.** Communication is a key component for the successful management of the uncertainty linked with the new advances in biomedicine and health innovation technologies. The decision-making process can be strengthened by early dialogue between the regulators and the regulated, as well as other stakeholders including patient groups, clinicians, and the representative public. A number of public-private partnerships are been set up with the goal to initiate and manage this dialogue. Consortia comprising government entities, companies, public laboratories and institutions as well as representatives from patient and consumer association are been developed. Further work will be needed to evaluate those partnerships and discuss their governance. Early collaboration between

scientists and industry could alleviate to some extent the technical and financial burdens of proof-of-concept studies, e.g. collaborations to generate data, use or analyse data, and to leverage data emerging from related clinical trials, including sharing patient samples or development of well-characterised populations.

- **Balancing the need for early access to innovative therapies with the need for comprehensive data on their benefits and risks.** This is a mounting challenge for regulators. Risk/benefit assessment should ideally continue throughout the entire life-cycle of a drug. To achieve this goal, various countries have created, or are considering creating, legislation and/or regulations to establish risk management systems to include the time when products are on the market. As risk-sharing access schemes are emerging, the sustainability of these schemes, as well as the many related methodological, economic and infrastructure issues, might be constructively explored through international exchange on good practice.

- **Continue to create better value-based agreements.** Emerging initiatives offer potential benefits to all main stakeholders: risk-sharing for the producer and user, cost reduction for the purchaser and market-share for the manufacturer. Not least of these benefits is that to patients: the benefit of having faster access to potentially superior life-saving products. The importance of policy support at different steps in the development of new solutions for health includes supporting ways of measuring the value of innovation (e.g. through test-beds: pilot projects that aim to validate and demonstrate value and help to create generic implementation models).

NOTES

[1] Dense sets of overlapping intellectual property rights.

[2] Situations which arise to prevent intellectual property being used e.g. patent thickets (see previous reference); people refusing to allow the use of key intellectual property; and/or intellectual property being kept in the approval process for a patent or license in the long-term, thereby blocking exploitation of other intellectual property.

[3] See more information on the website of the Foundation for the National Institute of Health at: www.fnih.org/work/key-initiatives/biomarkers-consortium.

[4] "A case-control study is an analytical study which compares individuals who have a specific disease ("cases") with a group of individuals without the disease ("controls")", information from the California Department of Public Health, see: www.ehib.org/faq.jsp?faq_key=34.

[5] "A cohort study is an analytical study in which individuals with differing exposures to a suspected factor are identified and then observed for the occurrence of certain health effects over some period, commonly years rather than weeks or months. The occurrence rates of the disease of interest are measured and related to estimated exposure levels. Cohort studies can either be performed prospectively or retrospectively from historical records?", information from the California Department of Public Health, see www.ehib.org/faq.jsp?faq_key=37 .

[6] See more information on the IRGC website at: www.irgc.org/risk-governance/irgc-risk-governance-framework/ (accessed April 2013).

[7] *In-vitro* fertilisation.

[8] See more information on the Stem Cell Forum Website at: www.stem-cell-forum.net/ISCF/.

[9] See more information on the UK Stem Cell Bank website at: www.ukstemcellbank.org.uk/.

[10] See more information on the Cambridge Stem Cell Institute website at: www.stemcells.cam.ac.uk/publications/publicationnews/regulationofstemcelltherapies.

[11] University of Massachusetts.

[12] See more information on the UK Biobank website at: www.ukbiobank.ac.uk.

[13] According to the OECD, Human Biobanks and Genetic Research Databases (HBGRDs) are structured resources that can be used for the purpose of genetic research, including: a) human biological materials and/or information generated from the analysis of the same; and b) extensive associated information (OECD, 2009b). Biobanks vary widely depending on the type of material they store (for example, they may collect DNA, tissue, living cells, associated data and any combination of these) and their purpose (e.g. therapeutic, research, clinical use etc.).

[14] See more information on the EMEA website at: www.emea.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp&mid=WC0b01ac05800292a4.

[15] This section is based on discussions at the OECD Workshop on "Better Health through Biomedicine: Innovative Governance" that was organised in September 2010 in Berlin as well as background material provided for the event; see: www.oecd.org/sti/biotech/workshoponbetterhealththroughbio-medicineinnovativegovernance.htm.

[16] See for example, OECD (2010), Biomedicine and Health Innovation: Synthesis Report, OECD, Paris.

[17] See more information on the US FDA website at: www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm201654.htm.

[18] See more information on the Germany Regenerative Medicine Initiative website at: www.rmig.org/welcome/.

[19] See more information on the EMEA website at: www.ema.europa.eu/ema/.

[20] Information collected from the European Commission website at: http://ec.europa.eu/health/human-use/clinical-trials/#rlctd (accessed in April 2013).

[21] See more information on the UK National Institute for Health Research website at: www.crncc.nihr.ac.uk/.

[22] Blueprint for Renewal II: Modernizing Canada's Regulatory System for Health Products and Food (2007) – Health Canada at: www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/index-eng.php.

[23] See more information on the Treasury Board of Canada Secretariat website at: www.tbs-sct.gc.ca/ri-qr/directive/directive01-eng.asp.

[24] See more information on the US National Institute of Health website at: www.nih.gov/news/health/feb2010/od-24.htm.

[25] Affiliation as of September 2010.

[26] This section is based on the OECD Workshop on "Better Health through Biomedicine: Innovative Governance" that was organised in September 2010 in Berlin, including background material provided for the event; see: www.oecd.org/sti/biotech/workshoponbetterhealththroughbio-medicineinnovative governance.htm.

[27] Board on Population Health and Public Health Practice (BPH) (2007), The Future of Drug Safety: Promoting and Protecting the Health of the Public, the National Academies Press.

[28] Affiliation as of September 2010.

[29] Affiliation as of September 2010.

[30] See more information at: www.myeloma-euronet.org/_dl/newsroom/Joint-statement-UK-NICE-decision-10-06.pdf.

[31] Novel risk-sharing schemes puts the spotlight on biomarkers (2007), Nature Reviews Drug Discovery Vol. 6, pp. 945.

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GLOSSARY

Biomarkers: A biomarker, or biological marker, is a measurable characteristic that reflects physiological, pharmacological or disease processes.

Combination Products: Combination products are therapeutic and diagnostic products that combine drugs, devices and/or biological products.

Genomics: The study of all of the nucleotide sequences, including structural genes, regulatory sequences, and noncoding DNA segments, in the chromosomes of an organism.

Microarrays: A microarray is a multiplex lab-on-a-chip.

Monoclonal antibodies: An antibody, produced by a single clone of cells grown in culture, that is both pure and specific and is capable of proliferating indefinitely to produce unlimited quantities of identical antibodies. Used in diagnosis, therapy, and biotechnology.

Nanodots: A nanodot is a microscopic cluster of several hundred nickel atoms that can be used to store extremely large amounts of data in a computer chip.

Nanoshell: A nanoshell is a type of spherical nanoparticle consisting of a dielectric core covered by a thin metallic shell (usually gold).

Proteomics: The analysis of the expression, localisations, functions and interactions of the proteins expressed by the genetic material of an organism.

Randomised clinical trial: A study in which the participants are assigned by chance to separate groups that compare different treatments.