

## FROM HARMONISATION TO COLLABORATION

### Introduction

Good morning ladies and gentleman – I feel honoured to have been invited to address such a distinguished audience and to participate in the discussion of what I feel is a fundamental issue facing the global innovation process. In my talk this morning, after reaffirming Australia's commitment to GHTF principles, I would like to review the benefits of global harmonisation, then discuss the challenges posed by emerging technologies, move to the risk management implications for Regulatory bodies of these challenges, and conclude by posing a question.

### Australia's Leadership Role

First, to Australia's commitment to Harmonisation.

In my previous role as CEO of Cochlear, I and the company were strong supporters of the Global Harmonisation Process in the Medical Device Regulatory domain. There was certainly a powerful business motivation for this support, given the plethora of regulatory agencies with which Cochlear was dealing, in selling its product to over 50 countries: the direct financial cost of addressing the different, albeit frustratingly similar, needs of the various Agencies was considerable; but the indirect cost in terms of diversion of resources and increased time to market was more significant.

Nevertheless, Cochlear also recognised the broader advantages of global regulatory harmonisation, and took on the responsibility, as a leader in the medical device industry in Australia, of contributing to industry's input into this process. Australia, too, through the TGA has taken on a leadership role in the regulatory arena. The TGA has reviewed its device regulation system – a system which was well established - and nonetheless supported reforms which achieve improved harmonisation, through incorporating aspects of European regulatory requirements. These include:

- Risk based classification of devices
- Defining quality, safety and performance effectiveness principles
- A Conformity Assessment Procedure

Manufacturers will still be regulated under the new scheme, but the focus will be on declarations of Conformity, and audit and inspection procedures.

This willingness to evolve its Regulatory legislation underscores Australia's commitment to the Global Harmonisation process. It has been very encouraging at this Conference to see that such a commitment is shared by so many Countries' Regulators, and to hear of the substantial progress made since the Harmonisation process began ten years' ago.

### **Benefits of Harmonisation**

The benefits of Harmonisation are many:

(i) I have already alluded to the improved *efficiency* in the use of scarce resources, and this applies to industry and regulators alike: both are resource constrained. For established companies, it will release resources to be reinvested in the R&D process.

(ii)As an extension of this point, there is improved likelihood that those devices developed by small, *start up ventures*, which are by definition resource constrained to the extent of living on the viability knife edge, will become more broadly available. The costs of obtaining Regulatory approval in multiple markets is a barrier to entry for smaller, newer companies.

(iii)The *time to market* of device products in a global sense will be improved, enabling the benefits of devices to become globally available sooner, with a consequent reduction in the overall social cost of the condition being treated, even after taking into account the sometimes high unit cost of the device in question. Given the rising proportion of GDP being consumed by health care costs, including the costs associated with longer life spans, there is a clear imperative to improve the global time to market of therapeutic devices.

(iv)Harmonisation will also promote greater global *equity* in the access to therapeutic devices: currently the cost and time involved in obtaining regulatory approval for countries with smaller domestic markets is an impediment, as the economic returns to industry may not justify the financial investment. That market is thus prevented from accessing the benefits of the device.

But there is a higher level advantage in seeking Global Harmonisation, and that is the foundation it lays: there is no doubt that the dialogue and cooperation, which are being engendered during this process, will equip the global Device Regulator community with the tools needed to meet the challenge posed by emerging technologies.

## **Emerging technologies**

What are these emerging technologies? Today I would like to discuss the nature of just three, but they are three platform technologies, the conjunction of which has significant implications for the very nature of medical devices. These platform technologies are Proteomics, Nanotechnology and Quantum Computing.

### (i) Proteomics

Whereas genomics is the study of genes and DNA in cells, proteomics takes the next critical step, being the study of the proteins, coded by genes and which control the myriad processes that occur within a cell. Although there are around 30,000 human genes, there will certainly turn out to be vastly more proteins, due to splicing and modifications to gene products. Proteomics has evolved to a point where key technologies can be assembled and applied to various tasks, including the identification of target proteins from complex biological systems for biological or structural experimentation. These tasks may result in, for example, personal profiling for prediction of the likelihood of disease susceptibility and/or clinical condition and/or whole organism drug response. The data from proteomic screens will be integrated into usable information for therapeutics, diagnostics and devices. Very quickly, however, the rate limiting step in discovery from proteomics will be the sorting of interesting leads from within the multitude of gene products – and the solution will lie in high-throughput methodologies, now being developed within the field of Bioinformatics.

### (ii) Nanotechnology

While advances in microtechnology continue to be remarkable, the way of the future is not in continuing to miniaturise, but rather to start from the opposite direction, and take individual atoms and build them up into molecular machines. Nanoscience is the research field of this small scale, and, as its name suggests, deals with the world on a nanometer scale ie in terms of billionths of metres. It combines physics, chemistry, biology and medicine and will enable us to develop technologies to arrange atoms and , in principle, build any structure we want. Companies such as IBM, Hitachi and HP already have patents for atom switches, atom relays and molecular switches.

Nevertheless, the intent of nanotechnology is not to manipulate one atom at a time because that would take too long. Rather, the objective is to develop self assembly technologies with molecular structures that can replicate themselves to order. In the biomedical context, nanotechnology is leading to new generations of prosthetic and medical implants with surfaces molecularly designed to interact with the body. Nanorobots are being developed to work within white blood cells; nanotechnology is being used to assist with gluing micro-sized components in tiny medical devices. There are also new models of drug delivery systems and new approaches to pharmaceuticals. In short a revolution is underway. In fact, the societal impact of nanotechnology is projected to exceed that of the silicon integrated circuit.

### (iii) Quantum computing

Related to nanotechnology is the field of quantum computing. In conventional computing, an eight bit register can hold one of 256 possible numbers or characters. In a quantum register of eight qubits, the register can hold all 256 numbers simultaneously and to different extents. This occurs because of properties of quantum systems known respectively as interference and entanglement:

- *Interference* is the property that the state of a quantum system depends upon all possible histories that may have led to that state.
- *Entanglement* is the property whereby measurements made on some parts will affect the results of measurements made on other parts, even though the various parts may be at great distances from each other.

Although interference and entanglement impart quantum systems with properties that are often counter-intuitive and which are at odds with our common sense notion of the world, they are well understood mathematically and have been experimentally verified. As far as we can tell, this is the way nature really is!

This field, having started as a theoretical construct in the late 1950s, is now emerging rapidly. IBM recently synthesized an artificial molecule and used it as the basis for a quantum computer. This was effectively a computer in a test-tube and therefore not scalable. In Australia, however, a team is close to delivering a device which represents achievement 90% along the way to developing a scalable quantum computer. The last step will be to demonstrate that *entanglement* is actually occurring. The benefits of quantum computing lie in its ability to process large amounts of information and solve previously intractable problems in useful timeframes. This has huge benefits in the field of bioinformatics, which itself underpins the biotechnology pipeline.

The implications for regulators dealing with this technology are best captured in an observation by Michael Nielsen, a leading researcher in the field. Nielsen says that quantum information theorists are like chess players, who know how to move the pieces, but not how to play the game well.

My purpose in spending some time describing these three areas is to demonstrate the extent to which they represent a step function change in complexity and breadth of understanding – and to highlight that they are moving rapidly out of the research domain into real world applications.

What are some of the implications for device Regulators?

(i) the first, I think, is the sheer number of products which will be presenting for regulatory approval. A lead indicator of this challenge can be seen if we look upstream in the innovation process to the activity in the patenting of IP. At a Conference on International Patent Systems held in Geneva in March, 400 delegates discussed the current crisis facing the International IP system: there was talk of severe problems of functionality, with patent offices having to handle enormous workloads in spite of constrained budgets. To gain some perspective of order of magnitude, Biotechnology as a sector now has revenues globally of more than US\$ 50bn with average R&D intensities of approx 40%. Delegates also referred to pressures from legal and technical perspectives, in addition to the workload dimension, and proposed international harmonisation and collaboration as providing the only viable solution. This observation reinforces the importance of the GHTF.

(ii) second, there will be further blurring around the definition of a medical device. It won't just be a question of whether the device also includes a drug delivery mechanism; it may be that the device is based on molecular "hardware", and the software may use quantum computing principles. This is the world of bio-devices. For Regulatory bodies, it will require increasing collaboration across disciplines and across organisational divisions.

(iii) another feature will be technology integration: devices will present regulators with exponentially more complex assessment, with the trend towards integrating technologies. Integration is being driven by the need to leverage the research done by others because the costs involved in being a technology maker in the Life Sciences field are prohibitive for most. Companies are therefore becoming technology takers, and forging alliances with organisations such as CSIRO, to access the necessary platform technologies. To reflect, and keep pace with, this development, we could possibly envisage a situation where Centres of Excellence develop among Regulatory bodies globally, with individual bodies becoming experts, and therefore reference sites in key technologies as they emerge, thereby leveraging Regulatory resources globally.

(iv) The volume of new products and shortening of technology cycle times will also lead to a need for Regulatory bodies to rely increasingly on the rigour of the design and development process in a company, (particularly that part which deals with hazard analysis and the identification of unintended consequences), coupled with a focus on post market surveillance and vigilance reporting. Complicating this approach, however, is the phenomenon that many emerging technologies are being developed in companies which are themselves 'emerging' and therefore do not have a track record of robust processes and systems on which Regulators can rely. This trend arises from the increasing willingness of inventors to proceed with start-up/seed capital rather than immediately seek the safety net of an existing larger corporation. Such larger companies, in turn, treat this as a research diversification strategy and consciously wait for technologies and products to survive this early stage before acquiring them.

In summary, the prospect facing Regulators is a situation of a greater volume of devices presented for approval, more complex devices, appearing in shorter time frames, often from companies with little track record. Against this will be an increase in the range, scope and benefit of the therapies offered. Inevitably, the Regulatory bodies will find themselves at the point of convergence of the risk/ benefit equation and will become de facto managers, if not custodians ,of risk, because of their independence and neutrality.

### **Risk Management**

This brings me to my final theme – risk management. I am particularly sensitised to this issue because of recent developments in Australia.

The issue of risk management brings into play the appropriate degree of precaution coupled with the prevailing degree of risk tolerance. For innovation to proceed, a balance must be found which enables these two dynamics to converge.

Taking an historical perspective, and looking to the nineteenth and early twentieth century, this convergence was not an issue. The precautionary principle was in its infancy and certainly risk to the individual and society took a clear second place to “progress”. The notion of caveat emptor was paramount. Innovation proceeded apace.

Gradually, however, the tort of negligence emerged and was accompanied by a general trend in tort law such that, as observed by the famous judge Lord Denning in 1949, “ the criterion of liability in tort is not so much culpability, but on whom the risk should fall”. This has become a critical distinction.

What we now observe, as we enter the twenty first century, is a much stronger precautionary principle on the part of suppliers of goods and services, and their associated regulators, with consequently more rigorous hazards analysis, but potentially pedantic over accuracy; on the other hand, we see a heightened reluctance on the part of individuals and society to accept risk, with a tightening in the standard underpinning the tort of negligence, from a *reasonable* duty of care to a *strict* duty of care. In essence, we see society increasingly rejecting the inevitability of possible adverse consequences risk when consuming goods and services, and responding in an increasingly punitive manner through litigation when risk materialises. The outcome, of course, is that those providing the goods and services are withdrawing them, or being forced to charge a price beyond the consumers' capacity to pay. The result is the same: access is denied.

Turning specifically to the field of medical devices, we now have diverging forces, with device regulations becoming tighter, and consumers approaching zero tolerance for risk, both of which are consistent, but are counter to the incredible rate of innovation in devices based on emerging technologies, which, by definition ,carry a higher level of ambient risk even after applying a reasonable degree of precaution.

We are facing a clear discontinuity and therefore a choice: do we proceed down the current path, and allow innovation to become stifled, or do we devise a methodology for managing our way through the risk/benefit equation? It is in this context that the Regulatory bodies, such as those represented here today, can play a pivotal role.

If we accept that we wish to facilitate continuing innovation, the starting point for finding a way forward is to recognise that we are operating within the constraints of a “complex system”, wherein there are causal relationships in place at any point in time, and causal loops determining these relationships over time.

This provides a framework within which to consider the interaction between precaution, scientific evaluation of potential hazards, and cost benefit analyses of alternative measures. Speaking at a recent Risk Management Conference in Belgium, a representative from the US Office of Information and Regulatory Affairs at the Office of Management and Budget proposed the following framework as an example of how a potential health risk could be explicitly managed by working through a series of questions. These questions seek to characterise the causal relationships within the complex system:

- What is the degree of certainty that the hazard exists?
- If it exists, and using a probability assessment, is it significant or negligible?
- Identify the population exposed to the hazard;
- Assess the number and quality of life years lost should the hazard materialise.

This framework ensures that sound science has a clear place in the risk evaluation process, though it has the weakness of appearing to define risk in terms of a number ie QALYs. The next, and balancing, phase in the process is to engage the public/consumer in this framework because they are a critical factor within this complex system and ultimately determine the tolerance for risk. This then raises the question of technological literacy.

Technological literacy is defined as, not only the ability to use the latest devices, but also an understanding of the risks and benefits of their use, and some comprehension of the engineering processes involved in their design and manufacture. Technological literacy brings with it an understanding that modern technology involves a complex interplay between

science, engineering, social impact, politics, ethics and law. Unfortunately, technological literacy is in short supply globally.

Just as an example, a report published earlier this year by the National Academy of Engineering and the National Research Council in the USA argued that, although America is a high technology nation, Americans – citizens and policy makers alike - are ill prepared to make decisions about technology in their own lives.

The implications of the rapid erosion of technological literacy are quite profound: one of the fundamental underpinnings of a sustainable democratic state is an educated population. This principle emerged strongly during the 18<sup>th</sup> Century, but it is arguable whether our education systems have kept pace with the nature and consequences of exploding knowledge. The “neglect” is probably greatest at the infants and primary level, where we may already have “lost” two generations of opportunity. Exacerbating this situation is the fact that expert knowledge of science and its derivative technologies is vested in a small elite who may, inadvertently, allow their own scientific interests to obscure implications for social policy and the common good. The ethical dilemmas posed by this conflict of interest are very confronting, and there is no doubt that Regulatory bodies will be increasingly drawn into the role of educator and arbitrator.

To sum up this section, perhaps I could draw on Dr Peter Sandman’s characterisation of risk: Sandman defines Risk = Hazard + Outrage. What I am suggesting is that Regulatory bodies could play a significant role in bringing risk back into a state of control – first, by ensuring that the “hazard” element is scoped using rigorous methodology, and within a framework such as I described earlier; and, second, by limiting “outrage” through providing information and education, thereby enabling informed interpretation of the hazard assessment outcome. If medical consumers perceive that the risk assessment process is in a state of control, they are

more likely to increase their overall acceptance of responsibility for risk ,which will thereby enable the flow of innovation to continue.

The question I would like to pose in concluding today – and while applauding the move towards harmonisation of the existing regulatory framework requirements for medical devices- is whether we are ready to take on the challenge of migrating to a new regulatory framework: one which can deal with the timeframes and inherent complexity, yet uncertainty, of emerging technologies; which can provide a bridge between the science/industry coalition and the medical consumer; which can provide a forum for identifying the technical and social risks of a particular technology, and then provide leadership in managing the risk assessment profile of medical device products approved for market release.

This new framework will require collaboration on a global scale among existing Regulatory bodies; it will require emerging Regulatory bodies to achieve a high entry level of expertise in order to participate and contribute; it will require a commitment to developing centres of excellence in agreed core technologies – and all of this is predicated on achieving mutual trust and cooperation on a scale beyond any envisaged to date.

I believe the question facing the Regulatory bodies is whether to take on this leadership role, co-opting researchers, industry and consumers, and finding a way through the risk/benefit dilemma facing us. The alternative is to be passive and allow innovation to be stifled, and the flow of available innovative device products reduced to a trickle.

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