Regulating interface science healthcare products: myths and uncertainties

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Whenever new technology emerges it brings with it concerns and uncertainties about whether or how it will need to be regulated, particularly when it is applied to human healthcare. Drawing on the recent history in the European Union (EU) of the regulation of cell-based medicinal products, and in particular tissue-engineered products, this paper explores the myths that persist around their regulation and speculates on whether the existing regulatory landscape in the EU is flexible enough to incorporate nanotechnology and other new technologies into healthcare products. By untangling these myths a number of clear conclusions are revealed that, when considered in the context of risk–benefit, make it clear that what hinders the uptake of new technology is not regulatory process but basic science.

Keywords: biomaterials; healthcare; regulation

1. INTRODUCTION

Whenever new technology emerges it brings with it concerns and uncertainties about whether or how it will need to be regulated. When the new technology is applied to human healthcare there is no doubt it will need to be regulated, but much doubt always arises as to how, and whether, existing regulatory routes are capable of dealing with the new technology, or, more importantly, whether the competent authorities have the expertise to understand the technology. These concerns continue to haunt the regenerative medicine industry, in particular cell-based medicinal products (CBMPs), yet many of the concerns are misunderstood by investors, product developers and other stakeholders, and consequently hinder progress.

Compared with the USA, the European Union (EU) is not a simple single jurisdiction but a union of individual member states each with its own national legal framework for medicinal products. From the very earliest days of the European project this was identified as a barrier to the free movement of medicines around the union as well as adding to the burden on industry to comply with disparate national rules. As early as 1965 the European Economic Community, as it was then, started to tackle this through Directive 65/65/EEC (European Council 1965) harmonizing the underlying requirements, including definitions and data requirements for market authorization (MA). These successful early attempts at harmonization showed that it was possible, and allowed the later more comprehensive harmonization of scientific principles achieved by the International Conference on Harmonization (ICH) between the EU, USA and Japan (ICH 2009).

Regulatory harmonization within the EU has continued with vigour ever since, most significantly by establishing the European Medicines Agency (EMA) in 1995 to administer a new centralized authorization procedure (European Council 1993b). However, the EU remains a complex region for pharmaceuticals since much of the regulation is decentralized because the member states have not relinquished their nationhood, but only agreed to cooperate to allow the free movement of goods, people and services. Consequently, activities within their national boundaries such as clinical trials remain their responsibility since they represent a health risk to their own citizens, and where products such as medicines need to be regulated they retain the right to consider the risks and benefits of the product. However, as new technologies arise, many, if not all, member states accept that their competent authorities may not have enough expertise to assess them, yet if they pooled this expertise across the EU this problem could be reduced. Furthermore, products for rare

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The regulatory framework for healthcare products in the EU is more flexible than it is often assumed, but it can be difficult to interpret the directives without experience; furthermore, without a clear understanding of the whole picture, erroneous conclusions can easily be drawn. Healthcare products (excluding products such as blood, organ transplantation and minimally manipulated cells) are regulated by one of two main routes: they are either medical devices or medicinal products. The legal definitions for these two possibilities are remarkably similar (Box 1), the main difference being the intended mechanism of action of the product. When the intended action is pharmacological, metabolic or immunological, then it is a medicine; when it is another mechanism (e.g. physical), it is a device. When more than one mechanism may be involved, then the principal intended mechanism must be determined. There are some rules that assist with difficult products: the medicines directive (European Parliament and Council 2001) is the ‘prime directive’ and in cases of doubt takes precedence (European Parliament and Council 2004a). The devices directive (European Council 1993a) specifically excludes human cells or tissues being devices, and a recent change clarifies that, where viable cells are present, their metabolic action is always considered to be the principal mode of action (European Parliament and Council 2007).

Box 1. EU legal definitions.

Medicinal product (Directive 2001/83/EC, Article 1.2 (b), as amended by Directive 2004/27/EC). ‘Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.’

Medical Device (Directive 93/42/EEC, Article 1 (2a)).

Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

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

The emergence of TE provides an interesting recent case study since these products are not expected to work by classical pharmacological mechanisms, but instead repair or replace a damaged tissue. This has led to one of the mythologies that persist to this day—that there was a regulatory gap in the EU legislation in that TE was not defined in law. It is true that a legal definition for TE did not exist before 2007 (European Parliament and Council 2007), but it is not true that this meant these products were therefore left in limbo. The main misconception arises from the scientific question of whether a TE product is a device or a medicine; many (including the US Food and Drug Administration (FDA)) initially thought of TE as being more akin to a device, and thus the US FDA licensed the first products primarily as devices requiring a pre-market approval (PMA). However, within the FDA expertise was drawn from other divisions, especially the Center for Biologics Evaluation and Research (CBER), since viable cells act more than just physically. Much confusion ensued about the situation in the EU; however, with the benefit of hindsight, it is easy to argue that this was unjustified. The main reason many considered there to be a gap is because they concluded the mechanism was not any of these and because the device directive specifically excludes human tissue or cells. However, to say the mechanism is purely physical is clearly nonsensical—why would anyone create a TE product to achieve something physical when it would be simpler and cheaper to use an inert material? Besides, cells are clearly metabolic, they react to their environment and metabolic tissues being devices, and a recent change clarifies
they can replicate themselves, so in part at least their mechanism of action must be metabolic otherwise why would you use them?

However, this is only part of the story, since like all legislation both directives have been amended numerous times. The current definition for a medical device has changed only subtly, and the key last sentence about the mechanism of action was present in the original version from 1993. However, the statement that medicines act through a pharmacological, immunological or metabolic action was only introduced in 2004 (European Parliament and Council 2004a), but, since this was an exclusion for devices, it stands to reason that it applied to medicines. The specific text in the devices directive that excludes human cells and tissues was also present, although the exact wording has also been altered subsequently. Returning to the definition of a medicine, although the action was not clarified until 2004 the definition of a substance remains unaltered since 1965 along with the examples given (article 1.3). Although it does not specifically mention cells or tissues, it includes ‘parts of organs’ as an example (European Council 1965). Without looking earlier than 1993, it is clear that, since then, viable cells (human or animal) were not considered to be medical devices and, so long as you could argue they restored, corrected or modified a physiological process, they were clearly medicines.

To further emphasize that there was no regulatory gap for TE or other CBMP, in April 2001 Novartis submitted a centralized marketing authorization application (MAA) for Apligraf to the European Medicines Agency (EMA; Business Wire 2001). At this time the EU did not even have a definition for somatic cell therapy, which was published in 2003 (European Commission 2003). Novartis presumably made a special request to the EMA since CBMPs were not on the list of mandatory products until 2009 (European Parliament and Council 2007), and were presumably accepted because it was new technology. Novartis withdrew the MAA owing to the breakdown of the business relationship with the manufacturer, Organogenesis (Krasner 2002). So why did the myth persist that TE products represented a regulatory gap?

The continuing myth is that this gap has now been plugged and we have a definition for TE; again, this is not really correct. The Commission did not actually define TE; it defined cell-based regenerative medicine, and then called it TE. For example, a single cell suspension of chondrocytes is now defined as tissue engineering in EU law, yet the widely accepted definition of TE is ‘use of a combination of cells, engineering, materials and methods to manufacture ex vivo living tissues and organs that can be implanted to improve or replace biological functions’ (BSI 2008). This definition describes a three-dimensional structured tissue, not a single cell suspension.

### 2.2. The regulatory pathway is unclear

The second myth that the regulatory route is unclear comes, perhaps in part, from a lack of clarity as to what is meant by regulatory route. Some, including the author, would view this as meaning the applicable legal regulatory framework and legal procedures that apply to that product category. Others may also view the specific scientific data requirements as part of the route, the guidelines that specify the expectations of the regulators; this might more accurately be defined as the data requirements.

Simply put, the requirements for any medicine are straightforward: demonstrate that it is of a consistent and appropriate quality, demonstrate it is safe, and demonstrate it is efficacious/potent. So long as the benefits outweigh the risks, it will get a licence. Taking the example of TE, the specific requirements have now been published (European Commission 2009), but in many ways they are no more enlightening. It must be remembered that the role of the regulator is not to dictate to the developer—regulators are not the experts in the product. Rather, the regulator’s role is to ensure that best practices and good science have been applied; one might call it peer review with teeth. The consequence of this might be called ‘regulatory creep’; as the science evolves and is applied to product development with good effect, it becomes expected of the next product, and filters through to guidelines and (more importantly) the expectations of assessors. The result is that all product developers are shooting at a (relatively slow) moving target, driven by science, innovation and thus expectation. Naturally this raises the possibility that, by ‘raising the bar’, well-resourced companies can effectively exclude poorly resourced ones. The lesson is that you cannot take your eye off the ball, and research and development never stops.

How can an emerging technology company solve the problem of determining data requirements? The simple answer is that the hurdle is not the regulation but rather the science; consequently, the solution can only come from research and development. Thus, again, the burden falls on the innovators to solve the problems; the tools and knowledge they need to do this are probably beyond all but the largest biotech company. The solution most probably lies in basic science, since the problems are usually founded in a poor understanding of the underlying science. However, the problem also often lies in a lack of understanding of the underlying principles of regulation, which are based on good science but require a particular state of mind. A good starting point is the harmonized ICH guidelines; these principles are common to much of the world, but may require considerable lateral thinking to apply to novel technology. It is also important to engage and educate the regulators early, so they are able to provide advice at critical steps; if you consider their role as peer reviewers it becomes obvious that you need to educate them. Although they operate within a legal framework, the role of the assessors, and ultimately the Committee for Human Medicinal Products (CHMP) and/or the Committee for Advanced Therapies (CAT), is to provide a ‘scientific opinion’; it is the European Commission that awards the licence.

### 2.3. Regulatory flexibility

With the historic lesson of TE in mind, it is worth speculating on the regulatory situation for other novel healthcare technologies such as nanotechnology. The first thing to consider for any new product is the
mechanism of action. If the product is a nano-robot that finds its way to the site of disease and releases a drug, it will be a medical (delivery) device. If, however, the product is an emulsion of a complex polymer that allows the polymer to be phagocytosed, processed and presented so that it finds its way to the site of disease and releases a drug, it is a medicine. If it is composed of two or more distinct parts with different mechanisms of action, it is a combination product, and each part should be assessed through the appropriate pathway, at least to a point. The whole must ultimately be assessed, and, as already mentioned, in the EU the medicines directive takes priority in cases of doubt and thus combination products will always be regulated primarily as medicines. With the emergence of TE, the EU authorities have already made headway with the procedural issues that this might bring and the terms of engagement of the EMA and the Notified Bodies (responsible for medical device assessment) have been drafted (CAT 2010b). Since nanotechnology ideas are already being applied to TE (see Kelleher & Vacanti 2010) these procedural issues should be well established by the time they submit an MAA.

The main barrier to regulatory flexibility is probably expertise; this comes back to the need to have early discussions with the regulators to educate them. It also requires the regulators to draw on outside expertise, hold workshops and actively engage the emerging industry. Compared with the US FDA, the EU authorities have often been aloof, but the new CAT has begun to reverse this trend and is actively engaging the industry through workshops to support guideline writing and meetings with interested parties (CAT 2010a).

2.4. Fast-track

All developers of healthcare products want to speed up product development, both in the belief they will benefit patients and to appease their investors. However, terms like ‘short-cut’ and ‘fast-track’ do not belong in the vocabulary of a regulatory professional, these terms are counter to the doctrine of regulation since they imply that quality, safety and efficacy will not be fully established. There are incidences where this is necessary, but these are few and far between and reserved for rare (orphan) indications or complicated indications where it is either unethical or simply not possible to accumulate a complete set of data in a reasonable period of time. This point is in part one of semantics; from a regulatory perspective there are no short-cuts, but there are many ways of prolonging development through poor strategy, poor understanding of data requirements and, perhaps most significant for emerging technologies, scientific uncertainties.

For a cash-strapped biotech company it may at first sight appear to be a coup when (as is not uncommon for CBMPs) the authorities agree that non-clinical animal studies would not be necessary before entering the clinic. CBMPs in particular pose significant challenges for animal models since key molecular interactions are often defective across species, and strong immune reactions can severely limit the duration of the study. The current best solutions involve the use of homologous models, which can consume considerable development time and are limited by the fact that they are only analogous to the medicinal product under development. Where the mechanism of action is suitably compatible it is generally necessary to resort to immunocompromised animals, but these are rarely completely devoid of an immune system and often exhibit atypical responses to foreign tissue. The final possibility can be the use of immunosuppression, but since many of these drugs have broad physiological activity they can interact with the test product in unpredictable ways such that results are inconclusive. However reasonable these arguments are, the fact remains that the absence of these data weakens the final data package, since these studies would normally provide significant insight into the mechanism of action, which may not be directly relevant because of species differences but at least provides direction and focus for other studies. Absence of these data creates uncertainty and weakens the data package and, as will be discussed later when weighing-up risk and benefit at MA, this uncertainty can make assessment of risk more difficult. Unless the clinical benefits are indisputable (which is uncommon), the absence of supporting animal data could result in a negative compounding. This, the clinical effect can take considerable time to be realized with CBMPs, and, since the assumption for many products is a long-term (if not permanent) effect, demonstrating long-term efficacy in the clinic before MA would mean such products would not be authorized in our lifetime. This can be managed through long-term follow-up commitments; but at the time of MA this adds to uncertainty, which might be mitigated to some degree with lifelong animal studies for instance. Aside from the loss of safety information, other vital lessons may not be learned that affect both quality and clinical development. From a business perspective non-clinical animal studies also help de-risk the transition to more expensive clinical studies; absence of these data shifts that risk to clinical development and, instead of reducing the risk of clinical failure, increases the likelihood.

Another word that slips into regulatory documentation that has no place in a science-led discussion is ‘belief’; belief implies faith and conviction, neither of which requires facts or data as evidence. It is easy when working hard for many years on a product to become blinded to negative data and focus on the positive and thus reach a biased conclusion. This is probably the main reason for regulation; deliberate fraud is thankfully rare, but biased ‘belief’ is common. To aid unbiased assessment, competent authorities attempt to ensure that assessors have no personal interests, and in many ways this makes regulatory assessment less biased than scientific peer review, where the reviewers who are active in the area are more likely to be biased. Removing bias is impossible, but, by removing the direct interests and ensuring that decision-making is disseminated, the system manages to minimize this as far as is reasonable. For the regulator, at least one bias does remain—that of the responsibility to safeguard public health—and this can lead to conservative assessment. This is understandable since the public back-lash from mistakes can be formidable. For the developer, this can be handled through regular scientific and regulatory due diligence using scientific advisory boards,
Regulatory block

It is hard to reconcile the widely held belief that regulation is stopping products getting to the market with the evidence. Firstly, in the EU only two CBMPs have been submitted through the centralized system (Apligraf and ChondroCelect); so for CBMPs in the EU, there have (as yet) been no negative opinions (although Apligraf was withdrawn for business reasons). There is often a strong perception that the US FDA has approved many cell-based products, but the list is short, with only two biologies licence applications (BLA) approved to date, along with four skin equivalents authorized through the PMA device route. Since, as has been mentioned, the EU authorities are less hands-on than the US FDA this naturally raises the question as to whether this is holding up approvals in the EU. It is too early to speculate for CBMPs, but analysis of drug approval trends does not suggest that approvals in the EU lag significantly behind those in the USA (Tsuji & Tsutani 2008; Graul et al. 2010). Consequently those products that have failed were not submitted in the EU either because they failed elsewhere, e.g. the FDA, or because the company terminated the product. It seems very unlikely that the developer would terminate the programme if the clinical data showed good efficacy, simply because they ‘thought’ the regulators would not license the product. It is more probable that the safety and efficacy data were not robust, even to the optimistic eye, or that other business issues led to termination of the project. Around 320 CBMPs are currently estimated to be in development and, as of November 2009, it is estimated that around 28 of these are in phase III (Buckler et al. 2010). In line with other medicinal categories we would expect the majority of these products to fail during clinical trials. In the absence of evidence that competent authorities are refusing licences to applicants (since there have been very few) we cannot currently speculate whether these products are more or less likely to succeed than other medicinal categories. Thus, we cannot reasonably blame the regulatory authorities for the lack of products on the market, but more probably, as already discussed, it is the result of an inadequate understanding of the underlying science.

Clinical trial approvals in the EU are not subject to the same level of rigour as an MAA; this is commensurate with the risk to public health since only a few selected and carefully monitored volunteers will be subjected to the product. The main focus for clinical trial assessment is the safety of the subjects and, in addition to scientific scrutiny, compliance with good clinical practice helps ensure this. Developers should be wary that they do not overlook this point since each trial is assessed primarily on its own merits. Although applications necessarily provide historical data to support the current request, they do not provide details of the company's strategy or what it intends to do next. Consequently, it is outside the regulators’ remit to give serious consideration to whether the trial will provide appropriate data for MAA; that is the responsibility of the developer. This is not to say that they might not object where issues are clearly apparent; rather, it means that you cannot assume that clinical trial authorization means your current approach is appropriate. For this you must request scientific advice and present not just what you have done, but what you intend to do and why. However, what can also be true is that the level of evidence required to get a truly novel investigational medicinal product into the clinic can be high. This is understandable: how do you manage an unknown risk? But here it is not just the regulators who can hold up progression to the clinic, but also ethics committees that represent many interested parties, and of course the media and politicians can all influence adoption of new technology. Consequently, new technologies often suffer more from influences outside the competent authority than from those inside them in the early stages.

3. RISK–BENEFIT AND UNCERTAINTY

Risk in this context usually means the probability of a medicine resulting in an adverse event multiplied by the severity of that event. For mainstream pharmaceuticals we can draw upon decades of understanding such that our estimate of risk in these instances is generally fairly certain, not least because we have established what the data requirements are to provide certainty to this judgement. When we consider biological products it is clear that proteins have become mainstream and the data requirements are now generally clear. But what of cells? We have a long history with transplantation, we understand much about organ failure is indisputable. However, the field of transplantation has mostly been about moving organs and the data requirements are now generally clear. But what of cells? We have a long history with transplantation, we understand much about transplant rejection and how to manage it, and the risk–benefit of transplantation for organ failure is indisputable. However, the field of transplantation has mostly been about moving organs and cells from a donor to a recipient with minimal manipulation. Cell therapy and tissue engineering bring uncertainties; expanding cells leads to many changes ranging from subtle differences in glycosylation through to morphological, phenotypic and functional changes depending on the cell and extent of culture and expansion. The impact of such changes is difficult to quantify, and consequently when considering risk–benefit for CBMPs or any novel technology uncertainty has to be factored in, since it affects the estimate of risk.

One could use the example of TGN1412 to make this point. The assumption that the primate studies were indicative of the human outcome, and that by giving a dose 1/50th of the dose that produced a response in a primate would be safe for man, led to overconfidence in the estimate of the starting dose. This confidence, based on more than 20 years of clinical experience with antibodies, resulted in four individuals receiving the antibody within the space of a few hours. With
the benefit of hindsight this was unwise, but it could be argued one mistake (but not the only one) was to assume certainty in the data and not factoring in uncertainty. When scientists at the National Institute of Biological Standards and Control analysed the clinical trial material it took them quite some time to develop in vitro assays that mimicked the in vivo responses seen in the test subjects (Stebbings et al. 2007). The lesson is inevitably caution, and recommendations were made and implemented following this incident (Duff 2006); the result will hopefully be that this does not happen again. The impact on those developing similar medicines is that they have to proceed slowly and cautiously, bringing obvious conflicts with business objectives.

All medicines must be considered based on their risk–benefit profile. At the extremes it is easy to judge this; an incurable cancer can be treated with medicines that have serious side effects if this leads to a cure or significant prolongation of a reasonable quality of life. At the other extreme, vaccines that prevent serious disease are given to large numbers of healthy individuals and even relatively rare complications can be considered unacceptable. In the UK, concerns over possible extremely rare complications of the MMR vaccine (Wakefield et al. 1998) led large groups of the public to lose faith and refuse to have their children vaccinated, even though by doing so they were accepting an even higher risk of their children contracting these diseases, a risk that increases exponentially as the numbers of non-immunized children increases (owing to the loss of so-called herd immunity). Risk is difficult to quantify and judge, and regulators err on the side of caution at least in part because the first duty of the state is to protect its people. It is fairly safe to say that products containing living cells (whether manipulated or not) pose at least as high a risk as blood products, and the history of blood products has many lessons to teach, contributing to what many refer to as the ‘endless list of regulations’. What is also fair to say is, unlike blood products, the risk-mitigating factors that we have in our armoury cannot easily be applied to viable cells without inactivating them. Furthermore, adventitious agents can take refuge within cells and possibly even replicate, mutate or recombine within them. This poses a risk, not just to the patient but to close contacts and possibly the wider community. Intensive farming of livestock has already led to a number of public health concerns; intensive culture of living cells will always be more risky than blood products or other biological medicinal products. In the EU, recent changes in the law and guidance from the EMA have attempted to encourage developers to take a risk-based approach. This is not really anything new, but is an attempt to formalize what is and should be done by developers throughout the product life cycle; a process that is particularly pertinent to biologics. Further discussion on this subject is beyond this article, but the same principles should apply to the development of nanotechnology medicines, especially since the risks may be unknown early on.

It is important for developers of all medicinal products, and even more so cutting-edge technology, to consider the rationale and risk of their therapeutic approach, both intrinsically and in the context of products currently available and in development by others. This is because the risk–benefit of a product has to take into account not just the data provided to support authorization, but currently available treatments for the indication. If products already on the market provide equivalent efficacy but have fewer side effects and/or pose a lower risk, then the new product will be unlikely to receive a positive opinion.

So what does the risk–benefit profile look like for nanotechnology medicines? It is too early to answer this question with any confidence. So-called ‘nanotechnology medicines’ such as Copaxone (Teva) show no obvious additional risk over other medicines, but perhaps not everyone would consider Copaxone a nanotechnology product. Nanotechnology devices such as buckyballs or buckytubes pose unknown risks, but thus far they have not been shown to self-replicate, although they can self-assemble (Kelleher & Vacanti 2010), but no doubt animal toxicity studies are able to evaluate their fate in the body. The main concerns aired so far are that some nanomaterials are very resistant to degradation in the body and the environment and thus their environmental impact may be a bigger concern than their toxicity in vivo. Such issues are already part of the assessment of medicines, although whether the current approach is adequate may need to be reconsidered as understanding increases.

It is therefore important for the developers of novel healthcare products to undertake a thorough risk assessment on their product, not only at the start but at regular intervals throughout development, to ensure that they continuously take account of new information. The difficulty of assessing risk has already been acknowledged, but unless attempted the uncertainties may not be clearly understood and subsequent research and development may not focus on solving the critical uncertainties that allow risk to be understood. Furthermore, it is important to keep an eye on competitors not just for disruptive technology, but to ensure that the rationale for using the novel technology remains sound since the inherent uncertainties of new technologies make assessment of the risk difficult. Consequently it is essential to confirm that the benefits outweigh the risk, not just of the novel medicine under development but also against other licensed medicinal products on the market.

4. CONCLUSION

Regulatory uncertainty does not stem from the absence of a legal framework. In the EU this framework is flexible enough to handle future innovation, although inevitably tweaks will be needed to categorize new products and clarify requirements. What will always be a challenge for new technology is the data requirements to demonstrate quality, safety and efficacy. The greatest challenge is to remove the uncertainty in these data, allowing the new technology to achieve a favourable risk–benefit profile.
The flexibility of the EU legal regulatory framework has been discussed in the context of TE, and the conclusions apply to other CBMPs that might be considered part of regenerative medicine. Since the current regulatory framework has already proved itself robust enough to encompass TE, it seems perfectly reasonable at present to assume that the same is true of nanotechnology or other novel technologies. As products emerge that do not clearly fit into the current system, the requirement for refinements is inevitable, but this does not necessarily mean their regulatory pathway is unclear. What remains (and will always remain) uncertain for new technology are the data requirements needed to demonstrate quality, safety and efficacy. Consequently, opinion leaders looking to support and foster innovative healthcare solutions should shift their focus away from the regulators and back to basic science since the only way to remove uncertainty is through a clearer understanding of the underlying science. As risk–benefit cannot easily be determined in the face of uncertainty; risk itself becomes uncertain, outweighing all but the most compelling benefit. By investing in basic research within both academic intuitions and industry, the uncertainty can be reduced, allowing new technology to be realized.

REFERENCES


