Chapter 6

Governance, regulation and risk management in synthetic biology

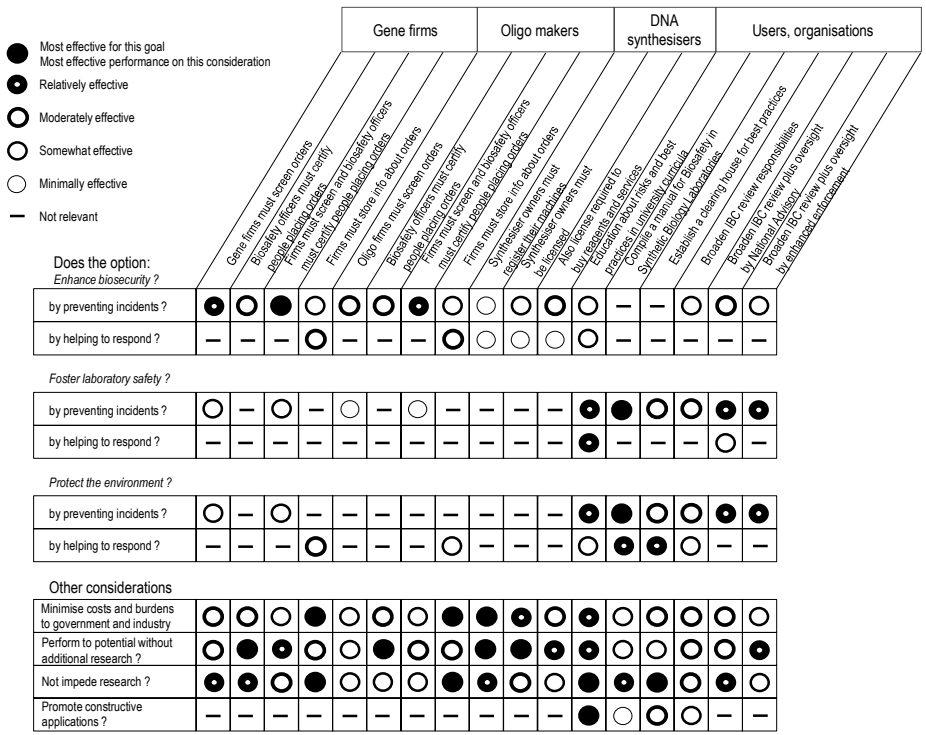
To date the regulation of synthetic biology is effectively the regulation of genetically modified organisms (GMOs). The thinking on whether this is adequate is polarised. The over-riding opinion of the synthetic biology community itself is that regulation is currently sufficient: it is felt that GMO regulation is already onerous and that further regulation may stifle research. Nevertheless, vigilance is required to ensure that any additional biosafety and biosecurity issues are discovered as early as possible and dealt with both rationally and rigorously. The main difference with GMO regulation may be the ability to order tailor-made DNA sequences. While the vast majority of these will be created for valid reasons by responsible individuals and institutions, the risk of mal-intentioned use calls for an inspection process and oversight. Governance and regulation must also take account of public opinion regarding synthetic biology, and the need for early and sustained public engagement is increasingly recognised. Potential international regulatory and governance conflicts could damage legitimate international trade. Therefore, even in parts of the world where there is little controversy, there would still be international trade issues.

Introduction

Many experts consider that synthetic biology is not significantly different from genetic engineering in terms of regulatory needs and that current regulation and the principles of risk assessment as applied to genetic engineering may be adequate for synthetic biology. For contained use (as opposed to deliberate release), synthetic biology in general is not expected to raise fundamentally new questions, even in the medium term (EPTA, 2011). However, a growing body of literature on how the nascent synthetic biology industry could be regulated (e.g. Kelle, 2009) can help to inform policy development.

The governance and regulation of synthetic biology concerns a wide range of potential stakeholders. Figure 6.1 summarises issues raised and some policy options. It covers DNA synthesis and synthesiser companies through to end users, as well as biosecurity, safety and environmental protection.

Figure 6.1. Summary of policy options in the regulation of synthetic biology



Source: Garfinkel, M.S., D. Endy, G.L. Epstein and R.M. Friedman (2007), "Synthetic Genomics Options for Governance", www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf.

Biosafety and biosecurity

Biosafety covers the range of policies and practices designed to protect workers and the environment from *unintentional* misapplications or the *accidental* release of hazardous laboratory agents or materials. Biosecurity is usually associated with the control of critical biological materials and information, to prevent *unauthorised* possession, misuse or *intentional* release.[1] More simply, the European Parliamentary Technology Assessment (EPTA, 2011) briefing note on synthetic biology terms biosafety as "keeping bad bugs from people" and biosecurity as "keeping bad people from bugs". Even though the difference between the two definitions may appear clear in theory, in practice the two tend to overlap. With the advance of synthetic biology, governments face biosafety and biosecurity challenges raised by synthetic biology.

For example, there are particular concerns about the use of software infrastructure to design parts by non-experts working from a home computer. While this does not engender any risk in itself, subsequent construction of a designed part may. Software use by the non-expert is not under the control of a laboratory or research environment and represents a challenging regulatory situation, as it will be difficult to monitor.

Biosafety and the user community

Synthetic biology is a scientific field that cannot be linked to a single professional branch. In addition to synthetic biologists, chemists, engineers, physicists and computer scientists are also involved in synthetic biology projects.

The biosafety problem in this respect is not necessarily related to a potentially malevolent intent, but rather to the lack of proper biosafety training or attitude (Schmidt et al., 2009). There is therefore a need for training programmes especially designed for non-synthetic biologist practitioners, such as standard microbiologists, synthetic chemists or computer engineers. In this respect the National Science Advisory Board for Biosecurity (NSABB) and the Industry Association Synthetic Biology (IASB) envisaged the development of a web-accessible advice portal for "experiments of concern", in order to provide scientific and biosafety-related advice for companies or single practitioners (IASB, 2008).

Biosafety and the eventual decentralisation of synthetic biology

The open source nature of synthetic biology creates both biosafety and biosecurity concerns. In the last two decades, the Internet has enormously expanded the potential to diffuse information "from the laboratory to the basement". In parallel, synthetic biologists have extensively used the Internet to increase the openness of this new life science, in line with an approach that favours openness, communication and innovation. The primary goals of this new approach were new ideas and better-informed public opin-

ion. As this eventually led to the release of scientific information outside the academic and scientific sphere, an increasing number of amateur practitioners are now likely to have little notion of biosafety (NSABB, 2010). The initial aim of enhancing innovation through public diffusion has therefore been slowly leading to a phenomenon now known as "garage biology" (Schmidt, 2008). At present a contained and relatively small issue, its importance may increase over time. At the very least, it requires monitoring by policy makers.

The potential for improper or malicious use of synthetic biology challenges the need for regulation, at least at the level of DNA synthesis. Among the greatest challenges facing those who develop such regulations will be weighing the costs and benefits of rules and developing an effective enforcement system. The situation in the United States and the European Union is described by Bar-Yam et al. (2012), bearing in mind that many other countries have their own procedures. Policies for regulating synthetic biology should aim to ensure the implementation of well-crafted regulations that do not hinder beneficial research.

DNA synthesis and biosecurity

The most critical difference for regulation between synthetic biology and genetic modification (GM) lies in the ability to make tailored DNA sequences. GM technology is restricted to complex laboratory operations. In synthetic biology, the design of DNA can theoretically be done from a computer in any location, without organisational regulation. Bügl (2007) argues that modern DNA synthesis challenges the existing recombinant DNA safety framework on two fronts:

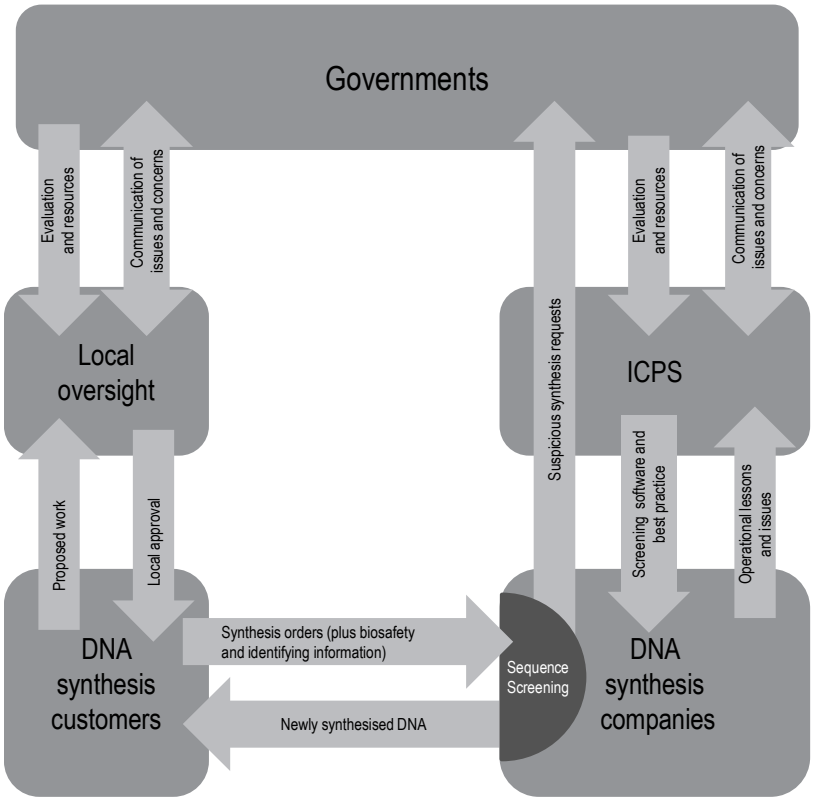
1. DNA can be readily designed in one location, constructed in a second and delivered to a third. The resulting use of the material can therefore take place far from its originators.
2. Synthesis may provide an effective alternative route for those who seek to obtain specific pathogens in order to cause harm, thereby circumnavigating national or international approaches to ensuring biosecurity.

Although much additional expertise would be needed to produce infectious agents from the resulting genetic material, such work may not be subject to review or oversight. The DNA synthesis industry requires regulatory protocols to ensure that it does not become a vehicle for biosafety/ biosecurity violations. The industry can only continue to advance and realise the potential of synthetic biology if it supports best practices in biological safety and security. See, for example, IASB on the effective deterrence and investigation of criminal uses of synthetic DNA. [2]

International regulation

A broader role for government policy is the achievement of international consensus. Harmonisation among countries is important. Otherwise potential violators of biosecurity regulations may simply transfer their design and construction activities to a less regulated country. Means of obtaining regulatory interaction among governments, synthesis companies and customers are summarised in Figure 6.2. It represents the collective views of all founding members of the International Consortium for Polynucleotide Synthesis as well as the individual opinions of members of the US Federal Bureau of Investigation, executives of several leading synthetic biology companies and members of academia.

Figure 6.2. A proposed framework for DNA synthesis regulation and oversight



Note: ICPS: International Consortium for Polynucleotide Synthesis.

Source: Bügl, H. (2007), "DNA synthesis and biological security", *Nature Biotechnology*, Vol. 25, pp. 627-629.

Comparisons of the regulatory instruments employed in the United States and the European Union help to see how broader international regulation may evolve. Table 6.1 shows that international regulation is virtually at the level of the Cartagena Protocol, which governs the trans-boundary movement of genetically modified organisms (GMOs).

Table 6.1. Analysis of regulatory coverage of safety and environmental risks of synthetic biology

Risk	International	United States	European Union
Transfer of genes	Cartagena Protocol on Biosafety	EPA and APHIS	Directive 2001/18/EC
Mutations, evolution and proliferation		EPA	Directive 2001/18/EC
Effects on ecosystem and other species	Cartagena Protocol on Biosafety	EPA and APHIS	Directive 2001/18/EC
Effect on biodiversity	Convention on Biological Diversity, Cartagena Protocol on Biosafety		Directive 2001/18/EC
Consumption risks		EPA (only for plant-incorporated pesticides)	Regulation 1829/2003
Risks to laboratory workers		NIH Guidelines	Directive 2009/41/EC Directive 2000/54/EC
Accidental release of laboratory strains		NIH Guidelines	Directive 2009/41/EC

APHIS: Animal and Plant Health Inspection Service, USDA; EPA: Environmental Protection Agency.

Source: Bar-Yam, S., J. et al., (2012), "The regulation of synthetic biology: a guide to United States and European Union regulations, rules and guidelines", SynBERC and iGEM Version 9.1, 10 January 2012.

Most GMO-exporting countries have not ratified the Cartagena Protocol. However, given that importing countries increasingly place restrictions on imports that are in line with the rules in the Protocol, the rules may have an impact on policies in exporting countries even if they have not ratified the agreement (Falkner, 2007). There is a body of opinion arguing that Annex III of the Cartagena Protocol should be modified to allow comparative safety assessments based on the properties of the introduced trait, rather than the current testing requirements (OECD, 2013).

A screening process for synthetic DNA manufacture and sale

The aim of a screening process is to avoid the intentional or unintentional sale of synthetic DNA to unreliable costumers.

By analysing US biological companies, Schmidt and Giersch (2011) concluded that the main aspects to be controlled are sequence screening for select agents to avoid synthesis of known pathogens or toxin-related DNA, customer screening to avoid shipment to dubious clients, and licensing of equipment and substances required for the synthesis of oligonucleotides.

Until recently, the role of governmental institutions in controlling synthetic DNA trade and production has been relatively marginal. However, this has changed slightly since US administrative bodies such as the NSABB have started to take a proactive role in promoting security standards in gene synthesis companies.

Documents such as the NSABB *Addressing Bio-security Concerns Related to the Synthesis of Select Agents* (NSABB, 2010) represent government efforts to try to address security at the institutional level. Nevertheless, government involvement is currently limited to recommendations.

The engagement of US governmental agencies could represent a step towards a more global approach to synthetic biology security. In explaining the objectives of its *Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA,*[3] the US Department of Health and Human Services (HHS) pointed out that "the Guidance was composed so that fundamental goals, provider responsibilities, and the screening framework could be considered for application by the international community". Box 6.1 lists some of the screening recommendations made by the HHS, as well those of a working paper co-ordinated by the Berkeley SynBio Policy Group.

Besides customer screening practices, a fairly new challenge needs regulatory attention: the phenomenon called "split orders". These are the alleged action of a mal-intentioned person or organisation that tries to circumvent the detection systems of DNA synthesis companies by splitting up one piece of DNA into many smaller, harmless-looking pieces and ordering them from a variety of companies (Schmidt and Giersch 2011). However, one of the barriers to this scenario is represented by synthetic biology itself: the complexity of assembling the pieces, along with transport uncertainties and environmental conditions, are considered serious obstacles. However, the split orders issue remains a potential problem that needs to be monitored, most of all at the international level.

Box 6.1. Synthetic DNA companies' screening processes

Following the guidance of the Department of Health and Human Services, the US government recommends that for every order companies should gather the following information: customer's full name and contact information; billing address and shipping address; and customer's institutional or corporate affiliation.

If the last of these is not relevant, providers are requested to pursue a follow-up screening process to verify the legitimacy of both the customer and the end user (if different).

In addition to these general requirements, the Berkeley working paper tries to identify procedures for improving the screening of customers and orders by gene synthesis companies. Once the traditional identification process has been carried out (e.g. nationality, employment or academic affiliation) companies should look at:

- Intended use: to confirm that the experiment is genuine and not a cover story; the customer should provide documents that can be used to judge the potential results of the experiment.
- Legitimacy: companies should evaluate the potential dual use of the gene requested.

Gene synthesis companies may rely on different investigative techniques:

- Direct evidence: direct contact with the customer to analyse the experiment, preferably in person, but most likely by telephone or email.
- Indirect evidence: companies can consult trusted contacts who know the researcher and his work.
- Signalling: The customer should provide evidence of the impracticability for terrorists to perform the same type of experiment. These assurances could include financial capability; proof that the work would be performed openly, so that a large number of scientists could scrutinise its developments; affiliation to a large, well-established and trustworthy company.
- Institutional control: companies might ask researchers' home institutions to monitor and report on the results of an experiment.

Source: Adapted from Maurer et al. (2009), "Making commercial biology safer: What the gene synthesis industry has learned about screening customers and orders", working paper, http://gspp.berkeley.edu/iths/Maurer_IASB_Screening.pdf.

Regulation and public opinion and engagement

Societal aspects of synthetic biology

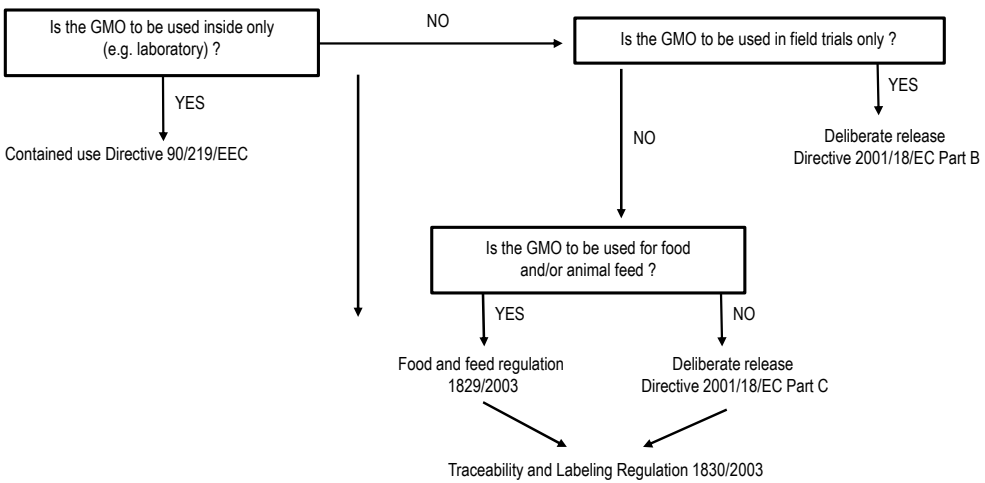
> "…if ever there were a science guaranteed to cause public alarm and outrage, this is it. Compared with conventional biotechnology and genetic engineering, the risks involved in synthetic biology are far scarier." (Ball, 2004, consultant editor for Nature)

> "Much of what is currently called synthetic biology is congruent with recombinant DNA technology discussed in Asilomar 30 years ago. This includes bacteria that express heterologous genes, proteins in which amino acids have been replaced, and cells with altered regulatory pathways. Placing a new name on an old technology does not create a new hazard." (Benner and Sismour, 2005)

These two quotations highlight an issue at the heart of the public engagement and acceptance debate that has shadowed GM technology. There has been an enduring disconnect between the scientific community, government and the public. Public and stakeholder pressures tend to reinforce demands for more regulation and stricter governance, related in the case of synthetic biology to biosafety, biosecurity, trade, global justice, and the morality of creating novel life forms (Tait, 2009). However, governance in the life sciences has led to an increasingly onerous and lengthy regulatory process that may eventually stultify innovation.

Given the serious concerns of public opinion regarding GMOs, Europe has adopted very stringent provisions. The legal framework is very complex and is based, among others, on EC directive 90/220/CEE (contained use) and EC Directive 2001/18/EC (deliberate release), (Figure 6.3).

Figure 6.3. Basic structure of EU GMO regulations



Source: Bar-Yam, S., J. et al., (2012), "The regulation of synthetic biology: a guide to United States and European Union regulations, rules and guidelines", SynBERC and iGEM Version 9.1, 10 January.

In the on-going debate about whether or not there is already enough regulation, it is worth re-emphasising that GM concerns have been much more of an issue in Europe than in other regions. It is not a significant issue in much of Asia, the Americas and the partner economies, and it is not clear whether these regions would agree that new or more regulation is required. The voice of civil society has traditionally been much stronger on the issue of GM in Europe; this is likely to be the case for synthetic biology as well. It is weaker in the United States, let alone in Asia or other parts of the Americas, where it barely registers as a political factor.

EU and US GMO regulations differ fundamentally in terms of the conceptual bases upon which they were established. In the United States, environmental legislation has been based on regulatory impact analysis which, by and large, is founded on the idea that "regulation must be based on learning: once more is known about a certain risk, regulation must be adjusted accordingly" (Aerni, 2006).

By contrast, in the European Union, environmental legislation has adopted the precautionary principle as the basis for evaluating the applicability of life science innovations. The principle relies on the premise that, if scientific data do not permit a full evaluation of the environmental risks of the introduction of a substance into the environment, the relevant authorities should block its diffusion (Aerni, 2006).

Yet, a recent EC report (European Commission, 2010) concluded that biotechnology, and in particular GMOs, are not *per se* more risky than conventional plant breeding technologies, after having spent more than EUR 300 million on more than 130 biosafety research projects, covering a period of more than 25 years, and involving more than 500 independent research groups.

As in the European Union, regulations in the United States do not deal with synthetic biology as such; typically, the processes and products of synthetic biology are covered by regulations that deal with GMOs. While it is often said that European regulations tend to be stricter than their US counterparts, the US situation is also complex and involves multiple agencies (National Institutes of Health, Environmental Protection Agency, US Department of Agriculture, Food and Drug Administration).

New agriculture and forestry: The defining public concerns?

The contained use of synthetic biology in research laboratories and in industrial bioreactors is much less likely to raise public concerns than deliberate or accidental release to the environment. After all, GM strategies for the production of new medicines have been used for decades (Goeddel et al.,

1979) and create little controversy. Fears arise when GM is moved beyond controlled environments and into the outdoors.

The forest products sector is looking for new opportunities to produce value-added products while securing access to emerging carbon capture markets (Sheppard et al., 2011). Extending the limits of conventional breeding of trees, a very slow and inefficient process, to realise faster and more accurate trait improvement for application in plantation forests (such as faster growth, improved pest and disease control), has the potential to lead to easier and cheaper development of goods, such as second-generation biofuels. However, because of public sentiment against GMOs, researchers and companies have used conventional and less efficient technologies (e.g. marker-assisted selection).

Synthetic biology, sustainability and the bioeconomy

Several countries and international bodies are developing the concept of a bioeconomy,[4] as evidenced by the publication of strategies, in the early months of 2012, by the United States (The White House, 2012) and the European Union (European Commission, 2012), and by earlier work by the OECD (2009). Bioeconomy strategies at national (e.g. Sweden and South Africa) and regional levels (e.g. Flanders) (Sormann, 2012) are under development. R&D in synthetic biology has initially addressed biofuels, which are themselves contentious, and products such as bio-based chemicals and plastics, which are hallmark products of a bioeconomy. A second phase, which involves a much broader spectrum of industry sectors, such as food, cosmetics, pharmaceuticals and medicine, is now emerging for synthetic biology.

Bioeconomy strategies focus on sustainability and the application of biotechnology to grand and societal challenges such as climate change mitigation, and energy and food security. The one indicator of sustainability that seems to be universally accepted is reduction of greenhouse gas (GHG) emissions. Many of the products of industrial biotechnology are designed to move away from dependence on fossil fuels and to reduce GHG emissions. A particular concern associated with industrial biotechnology, however, is the impact on land use of the large amounts of biomass required for non-food purposes. With the increasing number of applications of synthetic biology techniques to the manufacture of these products, the land use issue can be addressed by improving crop resistance to pests and drought, increasing yields of crops, using gas fermentations that do not require land for the production of biomass, and the industrialisation of photosynthesis (Pavanan et al., 2013).

Regulation of crops as bioreactors

For the controlled release of GM technology into the environment (fields, unless the plant cultivation is performed indoors), regulation is going to involve controversial policy decisions. Synthetic biology applications to plants in the field will inevitably face the same acceptance problems as GM, and the problems are similar to those already described for GM technologies. To the extent that the general public already has a negative opinion of transgenic plants, the notion that genetic engineering is against nature makes itself felt on regulators (Streiffer and Hedemann, 2005). Lack of communication among the regulatory bodies involved in research, biosafety and trade also hampers developments in this field (Ramessar et al., 2008).

The regulatory challenges for molecular farming and how they differ from those for first-generation transgenic crops were reviewed by Spok et al. (2008). The most important issue is to segregate GM crops from non-GM crops to prevent intermixing. It is very difficult to maintain complete segregation of GM and non-GM crops in open fields (USDA, 2006), even with stringent confinement. The European Parliament and the Council of the European Union have allowed GM presence of up to 0.5% in non-GM food or feed where the presence of the genetically modified material in non-GM material is technically unavoidable (European Parliament, 2003). For plant-made substances other than pharmaceuticals that do not pose hazardous risks, the threshold limit for contamination of non-GM crops is 0.9% (Spok, 2007).

Another important issue is labelling of GM products. However, mandatory labelling may not be economically justifiable and may not provide the consumer with the required information. Alternatively, information domains can be built to provide consumers with essential information related to GM content. A system that traces products in the market to their source and a good strategy for post-market monitoring and surveillance may also be a solution.

Regulatory conflicts and disconnects

Regulatory conflicts and disconnects are likely to be significant on at least three levels:

1. Between countries and regions, such as the EU, that apply the precautionary principle, with a focus on process as well as product and a presumption in favour of regulations, and the United States, where regulation is risk-based/evidence-based, the precautionary principle is not dominant, and there is no willingness to regulate process as well as product ("equivalence", which the European Union does not accept).

2. Within countries and regions depending on the mission and biases of different regulatory authorities (e.g. in the United States, the Environmental Protection Agency is likely to take a different approach to governance/regulation from that of the Food and Drug Administration or the Department of Agriculture).
3. At different levels within countries for countries with federal systems (such as the United States, Canada, Australia), where there could be regulatory conflicts between the federal government and the states/provinces, and between these and local jurisdictions.

Conclusion

As a public acceptance/perception issue synthetic biology is so closely related to the GM issue in Europe that it is impossible for synthetic biology to have a fresh start. It inevitably carries the GM baggage, but this has both positive and negative aspects. On the positive side, there are decades of experience in dealing with GM in terms of regulation and public engagement. Attempts to unblock the GM debate in various countries will also apply to synthetic biology, although progress in many locations has been extremely slow. The negative reaction to GM technology is not gradually disappearing as was expected and excessively demanding regulatory systems are not being modified on the basis of experience. The GM quagmire is to a great extent a European issue, and if it encompasses synthetic biology, it is very likely that its benefits will not be realised in Europe but in other regions.

Some argue that there is a need to reconsider how science is presented in communications with the public. Focus group research involving ordinary citizens in five European countries shows that the public resents decision-making procedures more than they oppose GM products as such (Levindow and Marris, 2001). The scientific community must take, and be seen to be taking, a lead in debating the implications of their research and must engage with society on the issues raised by synthetic biology (Balmer and Martin, 2008). For example, amateur scientists are stakeholders who are not often considered in the literature. In terms of dealing with risk, careful attention must be paid to the way synthetic biology skills diffuse to such groups. The consequences of this broader diffusion of biotechnology are not clear and should be investigated (Schmidt et al., 2009). In particular, ease of access to research tools and concepts increases the likelihood of unintentional effects by well-meaning institutionally based scientists or amateur biologists (Cho and Relman, 2010).

Notes

1. http://oba.od.nih.gov/biosecurity/pdf/NSABB%20SynBio%20DRAFT%20Report-FINAL%20(2)_6-7-10.pdf.
2. www.ia-sb.eu/go/synthetic-biology/.
3. www.phe.gov/Preparedness/legal/guidance/syndna/Documents/syndna-guidance.pdf.
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