

EPC CONFERENCE

Emerging biotechnology applications: EU, US and global regulatory perspectives

4-5 December 2005

Lille (France)

REPORT

1. BACKGROUND

In collaboration with the US Mission to the European Union and the European Commission, the European Policy Centre organised a two-day conference on “*Emerging biotechnology applications: EU, US, and global regulatory perspectives*” on 4 and 5 December 2005 in Lille, France.

Within the framework of its Better Regulation Programme, the EPC has contributed to increasing the level of convergence of regulations at the international level in general, and between the EU and US in particular. This conference was part of this programme and aimed to promote transatlantic regulatory convergence.

The conference was chaired by Stanley Crossick, Founding Chairman of the EPC, and this report was written by Richard Meads, the Rapporteur of the EPC’s Risk Forum. The event was held under Chatham House Rules.

2. OBJECTIVES

The conference focused on managing the risks and benefits from new and emerging applications of modern biotechnology in the EU and US. Its principal objectives were:

- To improve mutual understanding of the regulatory treatment of new and emerging biotechnology in the EU and US;
- To identify areas where approaches are similar and where they are different;
- To explore forward-looking options for enhanced regulatory convergence in the main biotechnology sectors (‘white’, ‘red’, and ‘green’).

3. PARTICIPANTS

Nearly 50 experts from Europe and the US attended the conference. A wide range of organisations were represented, including government services, businesses, non-governmental organisations (NGOs), academia, and related professions. The attendance list is included as an annex to this report.

4. WELCOME TO THE CONFERENCE

In his opening remarks, EPC Founding Chairman **Stanley Crossick** highlighted the importance of the objectives of the event and the extent of the EPC's support for transatlantic regulatory convergence. Over a period of nearly ten years, the EPC has organised 15 conferences on this issue.

This event built on the 2004 EU-US conference on biotechnology organised by the EPC, which was held in Perugia, Italy, and identified a number of issues of relevance to the future regulation of biotechnology in the US and EU. Specifically:

- Differences in regulatory approach are strongly influenced by different constitutional and regulatory cultures;
- The US is characterised by high levels of public trust in regulators but a lighter touch for federal government, leaving more to market forces and the courts to enforce compliance;
- Traditions and histories influence regulatory approaches, especially in relation to food, agriculture, and the food chain;
- In Europe, citizens may, in some areas, be more fearful of change than in the US;
- Amongst citizens in the Atlantic area, but especially in the EU, there is a lack of understanding of the nature of risk and that a risk-free society is not possible;
- All stakeholders need to communicate responsibly and citizens should have the opportunity to make informed choices, whenever possible;
- The politicisation of science should be avoided.

5. Keynote speeches

Robert Madelin, Director-General, Health and Consumer Protection Directorate-General, European Commission, argued that there is a need to connect the regulatory framework for biotechnology with wider regulatory trends, and to try to avoid seeing biotechnology as being unique.

Moreover, it is essential to recognise that promoting the development and diffusion of modern biotechnology depends on more than the design of the regulatory framework. Action is also needed to overcome the lack of risk capital for biotechnology investments in Europe and to ensure adequate public support for relevant science. In recognition of this more complex policy challenge, there has been an EU-wide strategy for biotechnology since 2002. A wide range of policy initiatives have also been initiated by the EU's Member States in the last ten years.

However, alongside these initiatives, Member States have also created regulatory barriers, most notably through decisions by a number of them to reject recommendations from the Commission and its agencies to approve "green biotechnology" (agricultural) products. Mr. Madelin explained that this was not a problem confined solely to biotechnology. Member States had, through the EU's comitology process, also rejected Commission recommendations in other areas, such as food additives.

The Director-General remained sceptical about the extent to which the Union could be characterised as being “anti-science” or the US as “pro-science”, arguing that most EU Member States were attempting to build up science-based regulatory systems.

He said there were a number of things that regulators and stakeholders could do to establish more effective and credible science-based regulatory systems. Science should be transparent and its findings made more understandable to citizens. Issues need to be addressed holistically and all concerns (including ethics, science, and economics) understood. This is of particular importance for “green biotechnology”. Industry too has a role to play. It needs to recognise the concerns of citizens and take these into account in its investment decisions. Risk management decisions take a wide range of factors into account, and are not solely determined by science.

Finally, Mr. Madelin identified a number of steps that could be taken to strengthen regulatory convergence between the EU and the US. Better links are needed at the operational level, including the creation of a network of risk assessors. This could help foster greater transatlantic understanding of risk assessment methodologies.

Madelyn Spirnak, Senior Advisor for Biotechnology, US Department of State, highlighted the benefits that modern biotechnology has brought to agriculture. After nearly ten years of commercial planting, more than eight million farmers in 17 countries grow biotech crops on over 200 million acres. Whilst the US remains the largest grower, 90% of users of agricultural biotechnology are in developing countries. This growth has been achieved, argued Ms. Spirnak, without any reliable documented harm to human or animal health. Indeed, the use of biotech crop has cut pesticide use, reduced greenhouse gases and created additional income for farmers.

In the US, the regulatory system is science-based and makes use of rigorous risk assessment. It focuses on risk rather than technologies, and assumes that biotechnology does not pose any intrinsic risks. This facilitates the development and use of agricultural biotechnology, protects citizens and creates consumer confidence. Today, more than 25% of all processed foods consumed in the US contain ingredients from transgenic crops.

Ms. Spirnak explained how the US was sharing its knowledge of agricultural biotechnology with developing countries. There is growing regional cooperation through organisations such as the APEC High-level Dialogue on Agricultural Biotechnology. The US government also supports policy-makers in developing countries through capacity- building programmes. Some internationally-led NGOs have opposed this, but their attempts to persuade African governments to adopt a more precautionary approach have been rejected, because of the importance of agriculture in many African economies.

There is, Ms. Spirnak argued, considerable convergence between the EU and US policies for supporting the use of biotechnology in developing countries. The two, for example, have a shared understanding of the potential economic gains from the adoption of transgenic crops in developing countries. But there are also differences in approach. She

said the EU needed to recognise the potential negative impact on developing countries of the perceived resistance of EU consumers and regulators to transgenic crops.

Only five agricultural biotechnology products have been approved by the EU since the mid-1990s, and Member States remain able to ban them despite the evidence of scientific risk assessments and European Court of Justice decisions. There is a risk that this will, over time, make the EU a less attractive location for investments in biotechnology, as well as leading to higher prices for meat and processed foods.

Discussion

Participants considered that public trust in regulators was a critical pre-condition for building consumer confidence in biotechnology, and argued that more effort was needed to improve risk communication.

Biotechnology in general, and agricultural biotechnology in particular, highlight important structural characteristics of the EU's approach towards implementing framework legislation.

Final implementation decisions about individual products or their uses are made using the comitology process. This is the risk management phase and normally takes place after a science-based risk assessment, often undertaken by one of the EU's new science-based agencies. Comitology involves the Member States meeting together to make the final decision and, as such, is a political process. This weakens the link between science and regulatory outcome and, because differing views amongst Member States sometimes produce unpredictable outcomes, leads to a lack of regulatory certainty. Over time, investors take account of such uncertainty and make changes in the allocation of capital. Lack of regulatory predictability increases the risks involved in developing new biotechnology products because it raises the overall risk profile of a project at a point when other factors (such as market potential and science) have become less uncertain.

Participants suggested the EU's comitology process could be reformed in a number of ways. More powers could be delegated to the Member States or to the Commission. Greater delegation to Member States could help increase transparency and accountability, but would fragment the Single Market. They also agreed that public concern about transgenic crops is a reality in the EU and must be recognised by investors. One cause is the lack of recognisable benefits for consumers; another is the association with food.

6. Regulating “red” biotechnology: maximising benefits and managing safety for new biomedical developments and applications

Background

Modern biotechnology is one of the most important enabling technologies used by the global pharmaceutical industry. Known as “red biotechnology”, it provides the basis for

new and improved therapeutic products, and is used extensively in drug development, drug production and diagnostics.

More than 160 biopharmaceutical products have already been approved to treat or help prevent heart attacks, strokes, multiple sclerosis, leukaemia, hepatitis, rheumatoid arthritis, breast cancer, diabetes, congestive heart failure, lymphoma, kidney cancer, cystic fibrosis, and other diseases. Over 250 million patients worldwide have benefited from bio-pharmaceutical products, and modern biotechnology provides more than half of the new compounds now in clinical trials.

Future application of modern biotechnology in the pharmaceutical sector may have the potential to meet unmet needs, to tailor medical treatments, and to prevent and better diagnose disease. However, ethical and safety concerns surround some new applications.

Professor Christopher-Paul Milne, Assistant Director, Tufts Center for the Study of Drug Development, Tufts University, USA, who moderated this session, highlighted the growing importance of biotechnology in drug development. Much of the investment in these technologies came, he explained from large pharmaceutical companies (“big pharma”), especially in the US. At the same time, the drug discovery ‘productivity’ of large pharmaceutical companies has fallen.

The reasons for this are unclear. One explanation is that this has been a temporary phenomenon: others see the trend as structural, and caused, in part, by the US regulatory system failing to keep up with drug discovery technologies. Another concern is that the ‘promise’ of biotechnology has not been met, with its impact primarily confined to improvements in the R&D process.

There are, Professor Milne explained, emerging concerns about the potential safety of new pharmaceuticals. There has been a slight upward trend in product withdrawals and, more importantly, because of biotech and other improvements in drug discovery techniques, companies have more clinical targets but fewer references for each target.

European perspective

Dr. Nils Behrndt, Deputy Head of Unit, Enterprise and Industry Directorate-General, European Commission, argued that there are two sides to the debate about future applications of biotechnology to human health. On one side, there are ideas that promise major improvements in quality of life and reductions in disease and premature deaths. But these are counter-balanced by concerns about safety and ethics. The future evolution of ‘red’ biotechnology in the Union will, he suggested, be influenced by the actions of wide range of actors, including industry, EU institutions, citizens and the Member States. A key concern at EU-level is striking an appropriate balance between promoting competitiveness and protecting public health. Ideally, these goals should not be antithetical.

Concerns about the safety of future biotech-based pharmaceuticals can be overcome, Dr. Behrndt argued, through a number of different strategies. One option (a passive approach) is to increase the number of clinical trials; another (more ‘active’) strategy involves greater use of new technologies such as pharmaco-genetics.

The EU’s legal framework for ‘red’ biotechnology has its origins in the 1960s, although major improvements have been made in the last decade. Recent changes include improved new pre-market authorisation processes (‘centralised’ process and the European Medicines Agency - EMEA – an EU agency for science-based risk assessment of new pharmaceuticals); improved intellectual property protection; an Orphan Drug regulation; new proposals to regulate advanced therapies; and guidelines for the development and testing of bio-similars (generic-type copies of bio-pharmaceuticals). In many respects, these changes mirror those that have occurred in the US, although the EU’s guidelines for bio-similars are more developed than those in the US.

The EU’s Orphan Drug rules, for example, are similar to those in place in the US and provide incentives to develop products for small markets. More than 300 products have been designated as ‘orphan’ products, over 20 authorisations have been granted and there has been an increase in relevant R&D.

An emerging issue in the EU is the regulation of advanced therapies. Many of these are, as Dr. Behrndt explained, based on modern biotech, and include technologies such as tissue-engineered products, gene and cell therapies. Ethical concerns surround some applications, and there are gaps and inconsistencies in the EU’s regulatory framework.

Dr Behrndt argued that there was a “regulatory gap” that threatened to undermine public confidence and investment. In response, the Union has developed new legislation providing a stable, clear, transparent procedure, involving the EMEA, centralised pre-market assessment, and post-marketing controls. But, in a change from the EU’s traditional approach, Member States will retain the right to refuse community marketing authorisations if they have ethical concerns - a political compromise that recognises the importance of ethical issues in this area.

US perspective

Dr. Eric Flamm, Senior Science Policy Advisor, Office of the Commissioner, US Food and Drug Administration (FDA), explained that in the US there is, generally, no special regulatory focus on biotechnology. As a general rule, US regulators focus solely on science and risks, rather than technologies.

Within the FDA, there is recognition of declining drug company productivity, falling numbers of new products, and the need to exploit changes in drug development technologies. Hence the decision to set up the Critical Path Initiative (CPI). This programme attempts to modernise the techniques and methods used to evaluate safety, efficacy and quality of medical products as they move from product selection and design

to mass manufacture. CPI aims to make use of biomedical discoveries, and focuses on clinical trials and manufacturing.

New regulatory approaches are also being developed to assess the risks of gene therapy. Threats to safety posed by these technologies have been highlighted by a number of well-known incidents. So far, the FDA has examined each new gene therapy on its merits, although a range of special safety and ethical considerations have been identified. These include toxicity risks, potential for uncontrolled heritable changes, and possible spread into the environment. New risk evaluation procedures have been developed. The greater consideration of ethical factors in this area illustrates some convergence with the approach taken by the EU to regulate similar technologies.

Finally, Dr. Flamm explained the US approach to regulating “bio-similars”. Unlike the EMEA, the FDA has yet to issue guidelines for assessing these products. It is unclear, argued Dr. Flamm, whether safe bio-similars can be placed on the market if they have not passed through a complete set of clinical trials and there are major concerns about the complexity of production of such products.

Discussion

Participants recognised the global lead taken by the EMEA to provide a regulatory framework for licensing bio-similars. The new guidelines provide for a case-by-case assessment and enable assessors to call for additional safety or efficacy data if appropriate.

It is, however, misleading to describe bio-similars as generics: the production of biopharmaceuticals poses safety and efficacy questions because of the complexities of the manufacturing processes. In the US, the FDA will not grant generic status to a product unless it can demonstrate equivalence.

Use of pharmaco-genomics will permit the development of drugs targeted at small sub-groups within the wider population. This could pose ethical issues, especially if such groups are defined on the basis of characteristics such as race. Evidence from the US and the EU suggests ethical issues are becoming increasingly important in influencing the overall regulatory framework for “red” biotechnology.

Trust issues will also become more important for regulators on both sides of the Atlantic as biotech-based technologies create new opportunities and concerns in healthcare. Public concerns about ethics and safety are important determinants of trust and the regulatory framework. Public officials and companies need to become more aware of the causes of negative risk perception, including issues such as ‘outrage’, ‘dread’, and stigma’. One way of improving public trust could be to increase investment in post-marketing surveillance. Business, it was pointed out, can help in this area.

Perceptions of the risk-benefit balance of different biotech applications appear to have an impact on the political response to new technologies by the EU's Member States. So far, it was suggested, life-saving medicines have been regarded, in general, as having a positive balance, whereas GM foods have not. This typology may change as ethical concerns become more important. Negative views about "green" biotechnology in some EU Member States may erode public support for new biotechnology applications in human healthcare.

7. Regulating "white" biotechnology: industrial applications, processes, product performance, and environmental clean-up

Background

"White" biotechnology, also known as industrial biotechnology, describes the use of micro-organisms and enzymes to produce goods and services, and to remediate environmental damage. It is the application of modern biotechnology for the sustainable and eco-efficient industrial production of chemicals, materials, and energy. It encompasses the use of biorenewables for feedstocks; the application of bioprocesses for production; and the development of bioproducts for markets.

Although successfully established in areas as diverse as antibiotics, vitamins, animal feed, starch, food and drink, and detergents, the use of industrial biotechnology is still in its infancy. Future applications could transform conventional processes and improve eco-efficiency in sectors such as energy, pulp and paper, chemicals, textiles, leather, metals, minerals, and waste treatment. White biotechnology provides the basis for cutting energy inputs, reducing waste and improving cost efficiency, quality and yields. It can also facilitate the use of a wide range of sustainable raw materials.

But there are also concerns about the use of these technologies. There are fears that, in some cases, using genetically-modified (GM) enzymes in production may lead to GM materials being present in final products, for example. It is also argued that the products of GM-based processing aids or GM-enhanced production processes should be clearly labelled, so as to enhance consumer choice.

Professor Wim Soetart, Laboratory for Industrial Microbiology and Biocatalysis, Department of Biochemical and Microbial Technology, Ghent University, Belgium, moderated this session.

European Perspective

Mark Cantley, Adviser for Biotechnology, Agriculture and Food, Research Directorate-General, European Commission, said the Commission supports the increased use of "white" biotechnology and is aware of its potential environmental benefits. There are, he

argued, a wide range of potential applications of these new technologies, including improved crops, enhanced production processes and bio-refineries. A biorefinery, for example, offers the potential to utilise a portfolio of chemical, thermal and biological processing tools to convert whole crops into fuels, chemicals, and materials.

Mr. Cantley argued that current and future regulation of “white” biotechnology in the EU is likely to be influenced by a range of factors. These include the EU’s existing biotechnology-relevant legislation, its Precautionary Principle and the nature of the application. Under existing EU rules, for example, regulation could be greatest for uses that involve modified crops or the food chain, because of the EU’s biotech-specific deliberate release, and traceability and labelling legislation. Uses that are confined to processing plants and that do not involve food could be subject to fewer rules, although they would need to comply with the EU’s contained release legislation.

The Union, in its life sciences and biotechnology strategy issued in 2002, recognised the need to update its biotech-specific regulatory framework. Possible areas for improvement identified include procedures for authorising the deliberate release of GMOs.

Yet the future application of EU regulation for “white” biotechnology remains unclear. In part, this is due to evolution of technology. But it is also linked to the potential future application of the EU’s Precautionary Principle.

In 2000, the Commission set out guidelines for the application of the Precautionary Principle, a risk management principle embedded in the EU Treaty. These guidelines require measures based on the precautionary principle to be proportional, non-discriminatory, consistent, based on an examination of potential benefits and costs, and subject to review. Moreover, measures should be capable of assigning responsibility for producing the scientific evidence necessary for a more comprehensive risk assessment. However, said Mr. Cantley, the guidelines have not been followed in all cases, leading to uncertainty about future application.

He also reminded participants that debates about the regulation of biotechnology take place within a global context. Recent global initiatives include, for example, the Biodiversity Convention and Cartagena Protocol. These too will influence the EU’s future regulation of “white” biotech applications.

Finally, the regulation of “white” biotechnology applications in the EU will be influenced by a wide range of non-scientific factors. There are several communities in public policy - including scientific, legal, economic, political and ethical communities - and each of these will play a role in shaping the regulation of “white” biotechnology in the EU.

US perspective

Dr. Flora Chow, Senior Chemist, Office of Pollution Prevention and Toxics, US Environmental Protection Agency (EPA), said that in the US, the EPA manages the risks

posed by new micro-organisms (a form of “white” biotechnology) through the provisions of the Toxic Substances Control Act (TSCA).

Uses of biotech regulated under the TSCA include the development and release of new GM industrial or speciality enzymes, and bioremediation. The development of new micro-organisms must be notified to the EPA using the procedures established for new chemical substances. These include exemptions on the basis of risk or if uses remain experimental.

The EPA has nearly ten years experience of regulating micro-organisms, and, as a result, has built up an understanding of the risks they pose. These include toxigenicity, pathogenicity, fugitive releases from closed systems, unintended release and gene transfer from environmental releases. In response, the EPA assesses the risks posed by new micro-organisms on a case-by-case basis and, where necessary, takes action to limit their use. The EPA will also consider taking action if petitioned by stakeholders. Restrictions have, for example, been introduced to protect vulnerable population groups.

Dr. Chow said the EPA had also become aware of some of the “risk-risk” issues that surround applications of “white” biotechnology. Increasingly, regulatory decision-making seeks to take these factors into account. In a recent example, a new GM enzyme posed unknown risks to human health and the environment, but provided major opportunities to reduce the use of traditional chemicals in oil recovery operations. Regulators faced the need to consider reduction of a known risk (exposure to chemicals) with possible new, additional risks. This is a more complex decision-making environment for risk managers.

Reforms to the regulatory requirements for “white” biotechnology are being considered by the EPA. More micro-organisms may be included within the exemptions set out in TSCA, but manufacturers will be required to demonstrate that the new materials “will not present” an unreasonable risk, and that conditions for physical containment and record-keeping will be met. Dr. Chow said these changes would, if introduced, protect public health whilst also strengthening incentives for the greater use of “white” biotechnology in the US.

Discussion

Participants highlighted a number of differences between the US and EU approach to the regulation of “white” biotechnology.

In the US, enzymes and micro-organisms are regulated as chemicals; there is no biotech-specific regulation. The focus is on risk, not technology. This provides a high level of regulatory predictability. In contrast, the EU has focused on developing technology-specific regulations. This leads, potentially, to problems for users of “white” biotechnology.

Within the EU, the greatest restrictions are placed on deliberate release of “white” biotech or uses in food production. Whilst the contained release controls appear to work well, there are considerable concerns about the potential application of the deliberate release, and food-related, biotech directives to “white” biotech. Boundaries between ‘contained’ and ‘deliberate’ release are, for example, difficult to define, and implementation of the relevant EU directives takes place at Member-State level, leading to uncertainty and inconsistency. The Union’s existing “technology-specific” approach may, it was pointed out, provide a framework for further restrictions on the use of “white” biotechnology.

Despite regulatory problems, there is evidence that some EU farmers are beginning to try to make use of “white” biotechnology to create added value crops. In some instances, it can produce products with the same performance as traditionally produced ones, but without any price advantages. Governments need to provide financial incentives for users to switch away from traditionally produced products. In the US, this can be achieved through federal government action; in the EU, competence remains with Member States.

Because of its potential to create cleaner, less harmful products, good regulation of “white” biotechnology requires decision-makers to consider both costs and benefits. In the US, this is possible because the TSCA is a risk-benefit statute: regulators are allowed to consider costs and benefits of decisions. In contrast, the focus in the EU is primarily on assessing and reducing risks to human health or the environment. Benefits can, however, be considered implicitly during the risk management decision-making process, although in most biotech-specific regulations there is no explicit recognition of this. An exception is the EU’s legislation on food and animal feed, which expressly allows regulators to consider “other legitimate factors” when making risk management decisions.

Negative attitudes to non-pharmaceutical uses of GM technologies in the EU could lead to stigmatisation of processes or materials that make use of modern biotechnology. In turn, this could persuade industrial users to limit investments in “white” biotechnology. Stigmatisation may also trigger the introduction by regulators of additional restrictions on uses of “white” biotechnology. There are, for example, continuing concerns in the EU about the use of unmodified enzymes produced using GM technologies in a wide range of production processes. So far, these have been considered to be processing aids so long as they do not form part of the final product.

8. Regulations and non-food GM crops and cross-overs between “white”, “green” and “red” biotechnology

Background

“Green biotechnology”, or the use of GM technology in the agricultural sector, is no longer confined to food crops. A range of sectors are beginning to make use of genetically modified, non-food outputs from the agricultural sector. Today, the most

important non-food GM crop is cotton. Worldwide 7.2 million hectares were grown in 2003, including 30% of production in India and 75% in the US.

Researchers are developing new, non-food GM crops for a wide range of sectors, including “red” and “white” uses of biotechnology. In the pharmaceutical sector, for example, alfalfa plants are being developed that can produce vaccine for foot and mouth disease. Known as “bio-pharming”, this may also include transgenic animals capable of producing inputs for pharmaceuticals. Other applications in development include GM potatoes, trees for the pulp and paper industry, and GM modified oilseed rape for use in the speciality chemical sector. GM technology is also being applied to the development of modified forms of biomass as a sustainable input for the energy sector.

These developments have raised considerable concerns about issues such as cross-contamination, animal welfare, ethics, choice, environmental damage, and threats to human health and public safety.

Dr. Jennifer Kuzma, Associate Director of the Center for Science, Technology, and Public Policy at the University of Minnesota, USA, who moderated the session, highlighted examples of the use of ‘green’ biotechnology for industrial and healthcare applications, noting that proteins could be produced in goat milk and inputs for vaccines could be provided by GM tomatoes.

In the US, the regulatory framework to manage the possible risks to human health and the environment posed by these new applications is already in place. It is based on a coordinated framework involving all relevant federal agencies and was established in the mid-1980s. It focuses on the potential risks posed by products rather than the technologies used to create them. As a result, no new biotech-specific legislation has been put in place in the US, although additional test guidelines have been established where appropriate. There are specific guidelines established by federal agencies to manage potential risks posed by field trials of new GM crops.

However, the development of non-food GM crops was not considered when the original regulatory framework was put in place in the US. There is a need, argued Dr. Kuzma, for US policy-makers to create stronger oversight mechanisms to ensure that all risks and concerns are considered fully and ensure coordination and coherence between different federal agencies. Better post-market monitoring of non-food GM crops is also needed.

Dr. Kuzma argued that future regulation of the potential risks and benefits posed by non-food GM crops needed to consider:

- Concerns about the possible impact of cross-pollination;
- A more complex risk-benefit distribution, including the wider social benefits of non-food GM crops, such as environmental gains, and impacts on the developing world;
- Public perceptions;
- Non-scientific factors, such as animal welfare and ethics.

European perspective

Dr. Paola Testori Coggi, Director, Health and Consumer Protection Directorate-General, European Commission, said that in the EU, “green” biotechnology is focused predominantly on improving the agronomic traits of crops, rather than providing consumer benefits or producing inputs for other sectors, such as healthcare or industry.

Moreover, only a small number of “green” biotech crops have been approved for use in the EU, and some sections of public opinion have yet to be convinced that such products offer any net benefit to society, even after taking into account possible benefits to farmers.

The Commission is, however, aware that future “green” biotech applications could provide inputs for “white” or “red” applications. Recently, the EU received an application to market a GM potato capable of providing starch to the pulp and paper industry.

Non-food GM crops may pose new challenges for risk assessors, including additional safety, nutritional, and environmental considerations. They may also create difficulties for risk managers in the EU, not least in determining what legislation applies in addition to the Union’s biotech-specific legislation.

On the basis of the EU’s current regulatory framework, non-food GM crops must comply with the requirements of two groups of regulations: the EU’s biotech-specific legislation, especially laws dealing with deliberate release of GMOs, traceability and labelling, and planting (co-existence); and sector-specific risk management legislation covering areas such as medicinal products, food, pesticides and biocides. Some exceptions might be possible, so long as relevant sectoral laws require risk assessments that meet the requirements set out in the main biotech-specific directives.

It was also possible that further new risk management requirements might be needed, such as new containment measures for plants used as ‘factories’ for pharmaceutical production or for transgenic animals.

US perspective

Dr. John Turner, Director, Policy Co-ordination Division, APHIS, US Department of Agriculture (USDA), said relevant US regulatory agencies had examined the risks posed by non-food GM crops and put in place appropriate regulatory guidelines for field trials. It is recognised that there is considerable interest in such crops because of their potential economic benefits, although only a small number are, as yet, in commercial production.

Since the late 1980s, the US has had stringent, science-based safety controls to manage the risks posed by all GM crops during field trials. Guidelines apply to all forms of GM crops and cover permits, separation distances, land use, segregation of equipment and

facilities, training, testing and inspections. There is also a high level of transparency, with details of all permits publicly available.

Specific regulatory requirements are, however, determined on a case-by-case basis. This enables regulators to establish larger separation distances where appropriate, and this approach has been used in a number of cases involving non-GM crops.

Dr. Turner explained that the overall framework has been used to manage more than 11,000 field trials, involving over 100 species of plants and micro-organisms at nearly 50,000 locations.

Crops can only be planted commercially when it can be demonstrated that they meet the safety standards of other similar non-GM crops. Once this has been achieved, then segregation, containment and other restrictions are removed. This is, Dr. Turner argued, a science-based approach that focuses on regulating risks rather than technologies.

Dr. Turner said this framework has been used successfully to manage the risks posed by GM food crops in the US. However, he recognised that non-food GM crops may pose additional challenges, especially if they are not intended for the food chain. In this case, safety standards may need to be established by other relevant regulations.

Discussion

Participants pointed out that in the EU, field trial approvals and conditions are determined by Member States. EU-level regulators are not involved and there is little consistency of approach across the Union.

Despite the rigorous and expensive conditions imposed by US regulators, the overall number of field trials carried out in the EU is likely to be substantially less than in the US, it was argued. In fact, US measures to control possible risks posed by field trials may exceed those used in the Union.

Regulatory controls on the commercialisation of non-food GM crops are significantly greater in the EU than in the US. In the US, such crops must comply with stringent controls on field trials and demonstrate that they meet the safety standards required of similar products produced using other technologies. After this has been achieved, there are no additional, biotech-specific regulatory costs. In contrast, non-food GM crops must meet the safety standards imposed by biotech-specific and sectoral laws, as well as the costs imposed by national co-existence guidelines. This final group of requirements limits available acreage, and raises production costs. In the EU, all commercial planting of non-food GM crops will be required to observe co-existence rules.

Non-food GM crops and the use of transgenic animals pose major risk perception issues for both US and EU policy-makers. Indeed, some scientists are still concerned about potential unintended consequences for the environment and human health of such

technologies. There are also ethical concerns. Regulators, industry, and other stakeholders need to discuss these and other concerns, through a process of dialogue. Used well, this could help identify emerging issues, build trust and shape future regulatory frameworks.

Market forces may also play a role in ‘regulating’ the potential risks posed by non-food GM crops. Some participants suggested that in the US, major food producers and retailers may require farmers to introduce containment and segregation measures, so as to avoid possible liability claims.

9. Biotechnology and Ethics: research choices, trade-offs and impacts on public welfare and developing countries

Background

In a growing number of cases, ethical and related regulatory factors influence biomedical research and the exploitation of biotechnology by developing countries.

Regulation of the development and exploitation of “red” biotechnology’ is increasingly influenced by ethical factors in a number of areas. These include using information about people including genetic data, demographic data, clinical records, and human tissues; carrying out new forms of research (stem cells, human embryos, and cloning); exploiting the results through, for example, patenting and other forms of Intellectual Property Rights (IPR); and carrying out clinical trials in developing countries

Public policy action to support, or hinder, the use of GM crops in developing countries has also become, in part, an issue influenced by ethical concerns. There are ethical and social issues involved in making GM crops readily and economically available to people in developing countries who want them. Access to relevant agricultural biotech is influenced by regulatory frameworks in the EU and the US, including IPR, market access, labelling and traceability rules.

Whilst many of the ethical and social issues are currently limited to the exploitation of GM food crops, similar problems are likely to be encountered once developing countries begin large-scale exploitation of non-food GM crops in “red” and “white” applications.

EU and US regulators need increasingly to consider the worldwide distribution of harms and benefits from “green” uses of biotechnology, as well as considering the impact of ethical factors on the exploitation of all forms of biotechnology by developing countries.

Professor Derek Burke, Vice-Chancellor, University of East Anglia, UK, who moderated the bioethics session observed that in Britain, regulators first become aware of bioethics when transgenic animals were developed for food production. This was seen by some influential groups as morally unacceptable, especially if it involved human genes. It was, moreover, seen as ‘unnatural’: an offence against nature. But not all groups share

these concerns, said Professor Burke. There is, he argued, a clash of values and attitudes: a conflict between moralistic and utilitarian beliefs, for example.

Policy-makers recognise that these concerns create new challenges for risk managers. Decisions about the best way to protect citizens and the environment from some risks faced challenges from citizens and potential loss of legitimacy, unless ethical factors are recognised and understood.

The bioethics debate has become more complex in recent years, as policy-makers and opinion-formers (such as the Nuffield Council for Bioethics, based in the UK) have begun to assess its scope and implications more rigorously. More emphasis is being placed on developing countries. Biotechnology, argued Professor Burke, has the potential to help developing countries solve fundamental problems, and there is a moral obligation for human beings in richer countries to help those in poorer ones.

EU perspective

An EU perspective on bioethics and “red” biotechnology, and the ethical issues surrounding biotech and developing countries was provided by **Professor Julian Kinderlerer**, Department of Law, University of Sheffield, UK, who chairs the European Group on Ethics (EGE), an advisory group to the European Commission President.

He identified a number of ethical issues that are likely to influence the regulation of “red” biotechnology in the EU, with three main areas of current concern: data privacy, clinical trials and developing countries, and stem cell research. He also outlined some of the ethical concerns surrounding test data and privacy.

Biotech advances make it possible for tests to be carried out that identify genetic disposition to certain diseases or conditions. Such tests are generally undertaken by individuals. But the results could have negative outcomes for other family members, even though they have not been involved in the tests. The freedoms of one group are potentially restricted without the exercise of choice, through the freely taken actions of others. It is possible that this problem may be resolved through existing law. EU data protection legislation does not, as a general rule, permit disclosure of data.

Another ethical problem facing EU regulators is the use of data from clinical trials in developing countries. In the Union, and other Organisation for Economic Cooperation and Development (OECD) countries, clinical trials are carried out within a highly regulated context, with a strong emphasis on informed consent.

In many developing countries, systems for ensuring informed consent of participants are sometimes poor or inadequate. Regulators, researchers and pharmaceutical companies need to consider, said Professor Kinderlerer, whether it is acceptable ethically to use clinical trials data obtained from countries that fail to meet standards of informed consent demanded in wealthy countries. No EU legislation currently deals with this issue.

The use of embryonic stem cells in research also poses ethical problems for EU regulators. Some Member States believe, principally on moral grounds, that it is immoral to use data obtained from stem cells. Others reject this but have, in most cases, created rigorous regulatory regimes to control relevant research. In the UK, for example, all research involving stem cells must be licensed. For the EU, there remains a major ethical problem: is it acceptable ethically for data produced from stem cell research to be used in countries that prohibit this activity? As yet, this problem has not been resolved.

There is an international legal framework to address the ethical issues surrounding the use of biotechnology by developing countries, based on the Biodiversity Treaty and Cartagena Protocol. Unlike the US approach to biotechnology, this framework focuses on technology rather than risk.

This, argued the Professor, has the potential to stigmatise biotechnology, despite its potential to alleviate hunger, disease and poverty. Already, there is evidence that some developing countries are reluctant to use agricultural biotech or to accept food aid from countries that grow GM crops. This is due to fears about long-term health risks, and concerns about access to EU markets for agricultural products.

Professor Kinderlerer expressed concern about the ethics of this approach. Continued starvation and poverty were, he argued, the most likely consequences for developing countries of taking a 'precautionary' approach to the use of agricultural biotechnology. In poor countries, the costs of inaction were likely to be significantly greater than the theoretical risks posed by agricultural biotechnology.

Finally, the problem of stigmatisation of agricultural biotechnology in the EU is becoming more complex because of the impact of market forces. Evidence from a number of leading food retailers suggests that 'voluntary' bans on the use of GM technology in the food chain are becoming more common. These have been established by retailers, in their role as 'gatekeepers', and represent a real barrier to trade between the EU and developing countries, said Professor Kinderlerer.

US perspective

Professor Robert Cook-Deegan, Director, Center for Genome Ethics, Law and Policy, Duke University, USA, focused on ethics within a policy context.

The US accounts for more than 40% of global spend by governments and not-for-profit organisations on biotech R&D. Governments and private companies in the eight largest industrial nations are the dominant investors in this area and own most biotech patents.

Although biotech Intellectual Property (IP) and research spending are concentrated in developed countries, biotech offers developing countries major opportunities, argued the Professor. Genomics has, for example, provided information that may facilitate the

development of effective vaccines against malaria. New patent laws and a lack of restrictions on stem cell research offer scientists in India the opportunity to develop new products for diseases. Antibody technologies offer developing countries the possibility of producing low-cost field detectors for a wide range of diseases.

Within this context, policy-makers in wealthy countries face a number of ethical issues, argued Professor Cook-Deegan. Specifically:

- Research priorities and the needs of developing countries;
- IP-related obstacles to the use of biotech by researchers in developing countries;
- Concentration of ownership of IP in wealthy countries and concerns about “distributive justice”;
- Incentives for researchers in wealthy countries to create IP for use in developing countries;
- Global access to research carried out in developing countries;
- Misuse of bio-technologies and the threat of bio-terrorism

Discussion

Participants pointed out that international bodies like the EU face difficulties when seeking to address ethical issues. Ethical values and philosophies frequently differ between nation states, because they are often rooted in social attitudes, beliefs and experiences.

A well-known typology of ethics identifies four different forms: utilitarian, fundamental rights, institutional, and intrinsic or moral. There are also different philosophical traditions. In the US, for example, there has been a strong utilitarian tradition, although this is now being challenged, in some states, by religious or moral values. In contrast, the UK has been more pragmatic, considering issues on a case-by-case basis. These differences make it difficult for international bodies to use ethical factors to make decisions that will be widely-accepted.

A potential problem for the EU is that the legal requirement to consider ethical factors may act to delay or obstruct the development of new products. Additional debates, and the introduction of non-scientific factors into risk management decision-making processes, create additional costs, slow down time to market and create uncertainty. This in turn reduces incentives for innovation, causes capital to be re-allocated, and limits the availability of socio-economic benefits from biotechnology to Europeans. Because of the nature of many of the potential benefits from new biotech applications, this is an ethical problem. There are, therefore, “ethics of delay”.

Some environmental activists in the industrial world have contributed to creating obstacles to biotechnology use in developing world, it was suggested. They have made decisions about the desirability of biotechnology on the basis of Western values and circumstances, without explicitly considering the problems facing developing countries.

EU policy-makers need to ensure that ethical debates about biotechnology are rigorous and “balanced”. To do this effectively, they need to consider its benefits as well as the risks. Too often, it was suggested, EU legislation focuses solely on managing risks rather than achieving a proper balance of risk and benefit. Potential beneficiaries of biotech include patients, developing countries and the environment. Agricultural biotechnology could, for example, to help developing countries alleviate starvation, poverty and disease. Used well, however, ethical advice can help policy-makers formulate additional relevant questions and highlight important ‘hidden’ benefits and the potential dangers of using a precautionary approach to the exploitation of new, enabling technologies.

10. Concluding Round Table on “Regulatory frameworks for emerging biotechnology applications: ways ahead”

European perspective

Professor Derek Burke of the University of East Anglia, UK, said there were important difference between the way in which the EU and the US have chosen to regulate biotechnology. This has led to trade frictions and, because the EU approach stigmatises and creates technology-specific regulatory obstacles, limits the availability to Europeans of the socio-economic benefits from biotech.

It is important to understand why different policies have been pursued and to consider whether differences of approach to regulating the risks posed by biotech will persist. The Professor suggested that the problems lie in the regulatory policies pursued in the EU and in the US, and not in science.

The EU has focused on regulating the use of the technology itself, whereas the US does not use a biotech-specific approach. Instead, US regulators make use of existing laws to manage risks. Moreover, the US approach is flexible and appears to accommodate changes in technology easily. Extensive use of guidelines within a well-established, science-based framework has, argued Professor Burke, created a regulatory context in the US that has encouraged innovation and investment, whilst ensuring high standards of protection for human health and the environment.

However, the regulation of biotechnology in the US and the EU also needed to be seen within a wider context. In the US, considerable emphasis is placed on the ‘ex post’ management of risks through personal responsibility of citizens, market mechanisms and the courts. This complements the ‘ex ante’ regulations put in place by Federal or State governments. In contrast, the EU focuses principally on ‘ex ante’ risk management by governments. These different approaches are the result of major differences in cultural, legal, and constitutional traditions between the EU and the US, argued Professor Burke.

Whilst these factors are important for understanding some of the differences between the US and EU approach to regulating biotechnology, they do not provide a complete

explanation. EU legislation is, he suggested, less science-based and more risk-averse, than in the US. This is the result of the interaction of a number of different issues.

Throughout the 1990s, the EU experienced a series of “regulatory failures” (such as BSE). These undermined public trust in scientific evidence and regulators, and contributed to increased risk aversion. At the same time, activists carefully exploited concerns surrounding the use of agricultural biotechnology. There were fears about contamination of the food chain, lack of choice, interfering with nature, and ethics. Taken together, these two groups of issues influenced the evolution of the EU’s approach to regulating biotechnology.

As a result, argued the Professor, the EU has created a regulatory framework for managing risks that potentially stigmatises the use of biotechnology and creates additional regulatory costs for innovators. This is a structural challenge facing EU policy-makers as they seek to manage the risks and benefits posed by emerging biotechnology applications.

US perspective

Dr. Murray Lumpkin, Deputy Commissioner, US Food and Drug Administration (FDA), outlined the transatlantic differences in risk tolerance and shifting perspectives within the FDA.

The FDA has begun to move away from focusing solely on protecting the public to also promoting health. To achieve this, he said, more emphasis needs to be placed on understanding the willingness of patients to accept risk. In part, this change in policy was influenced by the HIV debate in general, and concerns about access to new, innovative treatments in particular. In the US, this shift in emphasis has been achieved through changes within the regulatory framework; new primary legislation has not been required.

Achieving a greater understanding of patients’ risk tolerance has also been helped by the greater use of advisory committees. Federal law requires all agencies to have such committees. Representatives of consumers and patients sit on all FDA committees. Meetings are open to the public, and this helps to strengthen transparency and trust.

Advisory committees have also provided officials with an opportunity to gain greater insights into ethical concerns. One specific example involved the use of drugs in children, which was seen as unethical unless the same drugs had been tested on children. In this case, a specific advisory committee was set up to help inform the regulatory guidelines.

Finally, the FDA works closely with the EU’s EMEA and the international **ICH** initiative to strengthen technical links between regulators and risk assessors. Advances in biotechnology, argued Dr. Lumpkin, provide opportunities to speed up drug development through less emphasis on trial and error, and the provision of better, faster data.

Participation list

Nils Behrndt	European Commission (DG ENTR)
Thomas Bols	AMGEN
Derek Burke	University of East Anglia
Mark Cantley	European Commission (DG RTD)
Flora Chow	US Environmental Protection Agency
Stan Cohen	US Mission to the EU
Robert Cook-Deegan	Duke University
Elisabeth Cramaussel	US Mission to the EU
Stanley Crossick	European Policy Centre
Michèle Dastin-van Rijn	US Mission to the EU
Ignace Debuyne	American Soybean Association
Dominique Dejonckheere	Copa-Cogeca
Günther Eberz	Bayer AG
Trevor Evans	US Embassy to the United Kingdom
Eric Flamm	US Food and Drug Administration
Christopher Friend	Genetic Interest Group
Benjamin Gannon	Johnson & Johnson
Iain Gillespie	OECD
Peter Grosser	US Mission to the EU
Wills Hughes-Wilson	Genzyme
Lynn Johnson Langer	John Hopkins University
Josephine Johnston	The Hastings Center
Kristen Katzer	US Embassy to France
Julian Kinderlerer	Sheffield Institute of Biotech Law & Ethics
Jennifer Kuzma	University of Minnesota
Murray Lumpkin	US Food and Drug Administration
Robert Madelin	European Commission (DG SANCO)
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John Turner

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Etienne Vervaecke

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Emerging Biotechnology Enterprises

Nuffield Council on Bioethics

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US Mission to the EU

BASF AG

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