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Current EC and UK Legislation in Biotechnology*

Regulation in biotechnology in many countries is well developed. In order to have practical understanding of legislation it is necessary to understand the reasoning which occurred during their formation.

Why do we need legislation? What are the reasons for introducing regulation? There are the practical scientifically based regulations and controls brought about by understanding the hazards of a particular technology, and there are those brought about by political necessity.

Biosafety regulation has for many years been concerned with human health and safety. However recent public concern about pollution and the emergence of 'green' pressure groups has turned political thought towards the wider impact of modern technology on the environment, including the accidental and intentional introduction of microorganisms. Perception of risk and, the fear of not having control are two of the driving forces behind current regulation in biotechnology. In particular, the safety debate has been stimulated by the development of genetic modification techniques used with microorganisms.

Many of the regulations currently in place were developed for research needs during the advent of biotechnology. Most European and US Regulations are based to a large extent on the guidance resulting from the meeting in Asilomar in the United States in 1975, called by Prof. Paul Berg of Stanford University, to discuss the potential hazards of gene technology and to decide whether any restrictions should be placed or recombinant DNA research. Following this meeting regulations on the use of GMOs were first made in the US and in UK in 1978. The latter were based on a voluntary code of conduct and backed up by a series of guidance notes. All activities involving genetic manipulation were to be notified to an advisory body. In the U.S. this was the Recombinant Advisory Committee of the National Institutes of Health (NIHRAC) and in the U.K. the Advisory Committee on Genetic Modification (ACGM). It was these advisory bodies with representatives from academia, industry and government which formulated the early thinking on regulations and has led to the development of a safe industry. Today commercial exploitation of the technology is a reality and the next major products will be developed for applications in uncontained environments and this has led to a reappraisal of the legislation. Although biotechnology both new and traditional has an excellent safety record, there is concern that uncritical acceptance may increase the chances of mistakes.

Any accident of a serious nature, drawing publicity may damage experimentation - by imposing unrealistic legislative restrictions on work. It is essential that all interested parties ie. experts, industrialists and government agree a strategy in which workable regulations can be formulated. There can be no arguments that people and the environment must be protected but this must not stifle innovation. If biotechnology is to survive, grow and develop in todays political climate, everyone using it will have to take a long-term approach, developing relationships with **all** concerned parties.

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EC and UK Legislation

With reference to current legislation in the EC there are three directives which will affect work with microorganisms. The main directive concerning workers safety is the 'Protection of Workers from the Risks Related to Exposure to Biological Agents at Work' (1990)(1). This directive covers all biological agents and includes allergens. There are health surveillance requirements and such records may have to be kept for 40 years. The basis of the directive is the assessment of risks both from a conscious decision to work with an agent eg. laboratory workers and, to those who may be accidentally exposed to agents eg. sewage plant operatives; butchers. It applies to all risks but the assignment of biological agents into defined groups will be on the basis of risk infection, (much the same as the current U.K. regulations). However, it is likely that there will be a community classification of agents, probably produced by CEN - the European Standards Organisation.

To take the UK as an illustration, work with pathogens is controlled by the Advisory Committee on Dangerous Pathogens which is a tripartite committee of employer and employee representatives and specialist scientific and technical members. This committee produces guidance documents such as the 'Categorisation of pathogens according to hazard and categories of containment'(2). This classification of pathogens is based on the inherent hazard of the microorganism and it sets out corresponding levels of containment which are intended to compensate for the microbiological risks from the pathogens. The risk groups are defined by the following criteria:

(a) is the organism pathogenic for man/plants?
(b) is it hazardous to laboratory workers?
(c) is it transmissible in the community?
(d) is effective prophylaxis and treatment available?

Depending on the answers to these questions organisms have been placed in one of four risk groups.

1. An organism that is most unlikely to cause human disease.
2. A organism that **may** cause human disease and which might be a hazard to laboratory workers but is unlikely to spread in the community. Laboratory exposure rarely produces infection and effective prophylaxis and/or treatment is available eg. *Staphylococcus aureus.*
3. An organism that may cause severe human disease and presents a serious hazard to laboratory workers. It may present a risk of spread in the community but there is usually effective prophylaxis or treatment available. eg. *Francisella tularensis* (Type A), *Bacillus anthracis, Mycobacterium kansasii, Pseudomonas mallei, Rickettsia* spp., *Blastomyces dermatitidis, Trichophyton, Toxoplasma gondii,* lymphocytic choriomenigitis virus.
4. An organisms that causes **severe** human disease and is a serious hazard to laboratory workers. It may present a serious spread to the community and usually no effect prophylaxis or treatment. eg. Lassa, Ebola, Whitepox.

For each of these hazard groups there is a specified level of containment which details the type of equipment required and the standard of laboratory facility. These categorisations and containment levels are purely for the protection of workers and although this guidance is universally applicable it is irrelevant to most industrial practices. The EC Directive requires notification to a competent authority for the first time use of group 2/3/4 biological agents and for each subsequent use of all group 3/4 organisms with special consent for group 4.

Most microorganisms in use in industry are of the lowest hazard grouping, a few exceptions are in the pharmaceutical industry. There is an inherent incentive for industry to use organisms that pose a low risk, as this minimises regulatory constraints and reduces the need for expensive

plant and associated containment. Any problems or uncertainties regarding the industrial scale use of a particular organism should have been eliminated at the laboratory stage, well before scale-up. Relative to laboratory work there is nothing intrinsically more hazardous when industrial scale work is contemplated. It is the scale of operation that has increased leading to a greater possible escape volume, higher concentration and probable longer duration of exposure to the released organism. However many industries may now be using genetically modified organisms (GMOs).

Discussions on the safety of this technology date back to 1975 when Prof. Paul Berg of Stanford University called for a meeting of scientists to discuss the issues and implications prior to the continuation of such genetic research. Such a meeting was held in Asilomar in 1976 which gave rise to guidance on work with GMOs in the U.S. and the U.K. in 1978. All activities involving genetic modification were to be notified to an advisory committee, in the U.S. the Recombinant Advisory Committee of National Institute of Health (NIHRAC).

In the UK the Advisory Committee on Genetic Modification (ACGM) brought out regulations requiring that at each place of work where genetic modification is used a committee is set up to discuss all proposed work. This committee should comprise of representatives of all levels of workers not just the management and academics. The committees use what is known as the Brenner system in order to rate the hazards of a particular experiment in order to give a final risk factor. This risk factor then determines the level of containment required for the experiment and gives an indication of the precautions needed. If the hazard category is above 1 the work must be referred to the national advisory committee (ACGM). This system has worked extremely well in the UK for the last 13 years. The Brenner system, is based upon:

the host/vector system, its survival and mobilisation	– ACCESS
the expression in a system of the maximum production of foreign peptides	– EXPRESSION
infection or production of damaging products e.g. toxin	– DAMAGE

Assessment of an activity based on the three factors given previously may show that it falls into low containment levels or warrants only the use of good large-scale practice (GLSP).

GLSP was first formalised in a report on by the OECD 'Recombinant DNA Safety Considerations: Industrial, Agricultural and Environmental Applications of Organisms derived by Recombinant DNA Techniques', (3) and was based on existing good industrial practices. It has since been adopted by the EC in directive on the Contained-use of genetically modified organisms which is discussed later. It was a recommendation of the report that the large scale industrial application of rDNA techniques should, wherever possible utilise microorganisms that are intrinsically low risk. It also details containment levels for use by organisms which are deemed too hazardous to be used under GLSP. This is an invaluable reference for all those undertaking large scale rDNA work.

The two other EC directives in biotechnology which are aimed at protection of the environment as well as human health are 'Contained Use of Genetically Modified Microorganisms' and 'Deliberate Release to the Environment of Genetically Modified Organisms'(4). These became EC law at the end of April 1990 and have to be implemented by member states within 18 months. The contained-use directive requires those undertaking contained use operations to observe a general duty to take 'appropriate' measures to avoid adverse effects on human health and the environment and to conduct a risk assessment. For those working with large scale uses, GLSP or equivalent genetically modified microorganisms, principles of good occupational safety and hygiene must be followed.

A large portion of the guidance on large scale use is based on the recommendations of an OECD study on rDNA safety considerations. GLSP can be considered analagous to the concept of "minimal risk" which is used for toxic substances. In that context it can be considered as "a

level of exposure, below which the risks from exposure appear to merge with, and are comparable to, the general risks to which all workers are routinely exposed". Any potential hazards of industrial use of rDNA organisms are expected to be of the same nature as for other biological agents eg:

i) infection hazard,
ii) toxic or allergenic effect of the non-viable organism or its components,
iii) toxic, allergenic effect of its product,
iv) environmental effects.

Before work can commence certain notification and/or authorisation rules must be followed. Users should notify or seek the approval of a national competent authority when:

1. **First using an installation** - a maximum of 90 days in advance. Consent is required before proceeding if a Group II genetically modified microorganisms is to be used.
2. **For small scale work** (A operations)
   Group I (i.e. GLSP or equivalent) operations - records must be kept.
   Group II (all organisms not GLSP or equivalent) - notify, maximum of 60 days in advance.
3. **Large scale and manufacturing work** (B operations)
   Group I - notification, maximum of 60 days in advance.
   Group II - notification, maximum of 90 days in advance, consent is required for proceeding with the work.

The national competent authority will decide where it is necessary to draw up an emergency plan and inform local residents of any hazards. In addition a reporting system for accidents i.e. incidents involving a 'significant' and unintended release of GM microorganisms, must be established.

The deliberate release directive (5) is divided into several parts covering releases for research and development purposes and the placing on the market of products containing GMOs. The Annexes give details of the risk assessments to be made and submitted to the competent authority.

All three biotechnology EC directives will have to be implemented in Europe. This means new national laws in most cases some of the most comprehensive are likely to be in the UK, Germany, Netherlands and Denmark. In most countries of the EC there is Government body which deals with health and safety and, genetic manipulation issues, but these may not necessarily be one and the same. However as of 1991 there must be a competent authority to whom notifications of contained use and release together with substantial risk assessments must be submitted and these authorities in turn will, on certain issues, have to consult all member states before consent to use or release can be given. There will also be a committee of national experts from all EC countries to advise on releases and review legislation.

One of the tendencies with the recent legislation is biotechnology and environmental protection is the increase in horizontal legislation rather than the vertical product–based approach. Thus industry is faced with a complexity of regulation and several different channels through which it has to go in order to get a product approved and on the market.

US Legislation

The regulatory picture in the US is also not crystal clear. The 'Coordinated Framework for the Regulation of Biotechnology' (1986) (6) is a broad and complex policy which explains the application of existing statutes to the regulation of biotechnology and outlines the approach to interagency coordination in the US. A coordinating group, the Biotechnology Science Coordinating Committee (BSCC), has tried to provide a forum for coordinating issues in biotechnology

and resolving disagreements between federal agencies. The BSCC has also played a part in OECD deliberations and aided in the production and revision of the draft guidance on Good Developmental Practice. Within the US difficulty in clarifying policies for deliberate release persists, both with the EPA (Environmental Protection Agency) and the US Department of Agriculture (USDA). The USDA has its own Agricultural Biotechnology Research Advisory Committee which overlaps with other federal agencies such as the EPA and the USDA's own Animal and Plant Health Inspection Service. The Food and Drug Administration (FDA) which is largely responsible for evaluating products regards the use of biotechnology to produce regulated products as an extension, or refinement, of traditional techniques. There are no statutory provision or regulations that address biotechnology in general or genetic engineering in particular and no additional requirements are contemplated. The FDA is not the only body to adopt this regulatory approach, a similar philosophical stance was taken by the National Academy of Sciences 1987 policy statement on release of GMOs.

There have recently been calls for the Congress to survey biotechnology developments and agency regulation under existing statutes to consider whether current law is excessive or adequate. A recent report on National Biotechnology Policy from the Presidents Council on Competitiveness (1991) (7) stressed the need for coordinated action to improve competitiveness in biotechnology and review regulations in the area with a view to removing unnecessary regulatory burdens.

Conclusions

There is clearly still a need to develop an **international** effective regulatory regime in industrial microbiology backed by a workable risk assessment scheme and practical guidelines. It is essential to have a advisory body composed of **all** interested parties, a standardised risk assessment scheme and clear guidance on containment and handling procedures. Regulations can form the essential framework for a safe industry but are of little use if they cannot be understood and interpreted by workers and managers. It is essential that all interested parties agree on what the risks of biotechnology are so that important economic and socially useful products are not stifled by regulation.

Legislation/Guidance

EC	Protection of Workers	1990
	Contained Use	1990
	Deliberate Release	1990
UK	Pathogens	1990
	Genetic Modification	1989
	Environmental Protection	1990
USA	Guidelines for Research involving planned introduction into the environment of organisms with deliberately modified hereditary traits (USDA)	1991
	National Institutes of Health	
	– Guidelines on Pathogens	
	– rDNA research	1987
	– large-scale	
	Toxic Substances Control Act	
	– Microbial products of biotechnology (FDA)	1989

References

1. Commission of the European Community (1990). Council Directive on the protection of workers from the risks related to exposure to biological agents at work, 05 L 374 **33**, 31st December, Brussels.
2. Health and Safety Executive (1990) Advisory Committee on Dangerous Pathogens. Categorisation of pathogens according to hazard and categories of containment. Second Edition. London. HMSO.
3. OECD (1986): Recombinant DNA Safety Considerations. Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms derived by rDNA techniques. Paris: OECD.
4. Commission of the European Community (1990). 90/220/EEC Council Directive on the contained use of genetically modified microorganisms OJL 117 **33,** 8th May, Brussels.
5. Commission of the European Community (1990). 90/219/EEC Council Directive on the deliberate release to the environment of genetically modified organisms, OJL 117 **33**, 8th May, Brussels.
6. U.S. Federal Register (1986). Co-ordinated framework for regulation of biotechnology; announcement of policy and notice for public comment June **26,** Part II.
7. The Presidents Council on Competitiveness (1991). Report on National Biotechnology Policy. Chairman The Vice President Dan Quayle.

Aktualna legislacja biotechnologii w USA i Wspólnocie Europejskiej

Streszczenie

Stan prawny biotechnologii w Europie przedstawiono na przykładzie Wielkiej Brytanii; na tym tle pokrótce opisano sytuację w USA.

Biographical Note

After obtaining a first degree on Botany and Microbiology from the University of Wales, research was undertaken at the University of Newcastle-upon-Tyne in microbial ecology. This was followed by a years lectureship in Microbiology at Sunderland Polytechnic.

Research continued during a five year period at the University of Cologne, Germany, on biochemical, serological and genetic techniques for bacterial identification. Periods of time were spent at the laboratories of Prof. M. Mordarski, Wroclaw Poland (genetic relationships of actinomycetes) and Prof. R. Locci, Milan (taxonomy of streptoverticillia).

Currently a member of the U.K. National Microbiological Consultative Committee on Safety; the Chemical Industries Association Biotechnology task force; Council member of the BioIndustry Association and Chairman of the Regulatory Affairs Committee. Member of the U.K. Advisory Committee on Genetic Modification (ACGM) and the Advisory Committee on Releases to the Environment (ACRE). Formerly, expert to a study group of the Economic and Social Committee of the EC on the 'Protection of Workers against Biological Agents' directive; Member of the Editorial Board of the Journal of General Microbiology and former Committee member (SGM).

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