# REGULATORY OVERSIGHT OF THE USE OF GENETICALLY MODIFIED ORGANISMS

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## BACKGROUND

For centuries man has been involved in the utilisation and improvement of biological systems or processes to produce a vast number of products, for example, beer, wine and bread. In general these processes relied up on selecting particular strains either through natural selection or through crude selection methods to produce desirable end products such as a better beer or an improved wheat varieties. The entire process may have taken a number of years to reach the desired stage and the nature of the end product was sometimes uncertain. However, this technology, defined as traditional biotechnology, has developed over the years and been applied to an ever increasing number of industrial sectors, eg agriculture, chemical, waste and pharmaceutical areas.

With the discovery of the structure of deoxyribonucleic acid (DNA) as the genetic blueprint of life, significant advances in biotechnology took place which culminated in the early 1970s with the successful introduction of genetic material from one organism into another in which it could not occur naturally Thus commenced a new era of biotechnology involving techniques of genetic modification or recombinant DNA(rDNA). These techniques offered significant advantages in terms of specificity and speed over the traditional methods.

The early days of the development of techniques involving genetic modification were times of uncertainty. Concerns sprang from the feeling of many within the scientific community that their work might expose both them and the wider world to new and unknown hazards. Could scientists really predict the outcome of their 'engineering' of nucleic acids? Fears developed, fuelled by some outrageous claims of danger in the media, that novel organisms would be produced; bacteria that could transmit cancer or devastate major economic crops. It has to be said that with the benefit of hindsight, after close to eighteen years' experience of genetic manipulation, we now view such fears for human health and safety in a more rational way, but at the time they were absolutely correct and proper matters for concern. It was only by addressing these questions that this technology was able to progress to the level of commercial exploitation that we have today.

The period from 1973 to 1975 saw what became and has remained an unusual sight in the development of occupational safety, an industry, in this case the laboratory community, calling for a moratorium in its own work so that safety could be addressed. This is in contrast with so much of the history of health and safety, where significant progress has occurred only after disaster has already taken place.

Concerns regarding the developments by which restriction endonucleases could be used to produce hybrid DNA with a biological activity of an unpredictable nature were first raised at the Gordon Research Conference on Nucleic Acids held in 1973. Singer and Soll[1] called for the US National Academy of Sciences to consider the potential hazards of recombinant (rDNA) DNA to workers and the public. The following year saw a letter published in 'Science', calling for a partial halt to rDNA experiments. The 'Berg letter'[2] highlighted two areas of work: (a) the creation of new autonomously replicating plasmids that might transfer determinants of drug resistance or of toxin production, and (b) the linkage of oncogenic and animal viral DNA to autonomously replicating elements. The authors called for the establishment of an advisory committee to oversee rDNA work and to devise guidance for safe systems of work.

The 'Berg letter' prompted a rapid and mixed set of responses. There was a strong commitment from the National Institutes of Health to the proposals, but outright opposition came from others who saw them as an 'interference of their freedom to carry out scientific research'. The scientific authorities did respond to the call for a moratorium. Within a month, the UK Research Councils had established a review to assess the potential benefits and hazards of 'genetic manipulation' and the UK Medical Research Council instructed its staff to comply with the moratorium. A working party under Lord Ashby reported in 1974 with recommendations that enormous potential benefit existed in the technology but cautioned that this could only be realised with due regard to safety.

This was reinforced in 1975 by the Asilomar Conference in California. It was concluded that certain genetic manipulation work could go ahead provided that strict safety precautions were met, but for other work, the moratorium remained until the question of safety guidelines could be addressed. Some classes of experiment were judged to be potentially so hazardous that they were not to be allowed to proceed under any circumstances(3).

Asilomar brought the concept of biological containment, the use of viral or bacterial hosts for genetic research that are incapable of surviving beyond the laboratory as a result of mutations encoding such properties as temperature sensitivity, cell wall deficiencies, nutrient dependency, etc. Asilomar also recognised a need for classes of physical containment, three graded levels of safety precautions that should be applied to genetic manipulation experiments, dependent on the level of hazard. Thus, the concept of defined control replaced that of the moratorium.

The National Institute of Health established the Recombinant DNA Advisory Committee (RAC) which then held its first meeting the day after the Asilomar conference closed. During 1975, draft guidelines were produced which containment for E.coli K12 host-vector systems and specified appropriate levels of physical containment. This approach set the basic framework on which guidance and regulation was to be developed worldwide for the next decade.

THE DEVELOPMENT OF A REGULATORY SYSTEM IN THE UK

The control of potential hazards in this technology has been established within a regulatory system that we believe has allowed the technology to be developed without hindrance whilst, at the same time, maintaining our high standards for health and safety.

To this end it may be appropriate to start with the basic premise of our approach - that there is nothing special about recombinant DNA technology, genetic modification or whatever the descriptive is - as far as the Health and Safety Executive is concerned. The health and safety implications for workers and for the general public from all workplace activities are controlled under the provisions of the Health and Safety at Work etc Act which came into force in 1975.

The Health and Safety at Work etc Act established the Health and Safety Commission and Executive. Its main regulatory impact was that it established general duties which are imposed upon all those who operate undertakings. Earlier legislation, in contrast, dealt predominantly with provisions for factories leaving many millions of workers without health and safety cover under the law. The duties of the Health and Safety at Work etc Act apply to all employers, the self-employed and also to workers and in the main they are qualified by the concept of reasonable practicability - a duty to protect health and safety by going as far as possible as cost, trouble and time allows, proportionate to the level of risk. This balance of risk and effort which has its basis in case law over 40 years ago is a recurring theme in respect to the UK regulatory scene.

The 1974 Act gives us our powers, powers to make regulations, powers to inspect and to take enforcement action, including the power to prosecute. Biotechnology activities are covered by the legal provisions of the Act just as in any other industry, and as the Act was being implemented in the UK, so the concerns of Asilomar had just impacted upon the UK scientific community.

As mentioned above, the reaction in the UK had been rapid, with issue of the Ashby Report. This was followed within a year by the Williams Report which contained a code of practice and recommended laboratory containment measures for genetic manipulation work. It was this group under Professor Williams who recommended to HSE the need to establish a control system in which notification to the HSE of work involving genetic manipulation would be made a statutory requirement.

1976 saw the establishment of the Genetic Manipulation Advisory Group (GMAG) set up initially to assist those working in this field towards safe systems of work. GMAG issued the first detailed guidance on risk assessment and on laboratory containment and the Group became established as a source of reliable guidance for users.

It was in 1978 that the regulatory package recommended by the Williams Committee became law. The Health and Safety (Genetic Manipulation) Regulations introduced requirements for the notification of such work to GMAG and the HSE. This type of notification or registration of certain work activities has been used by HSE and its Factory Inspectorate

predecessors in various industries and in this case, this meant that the guidance issued by the Advisory Group could be used by the HSE's inspectors on their site visits as the standard by which compliance with the Health and Safety at Work etc Act could be judged.

This established the three stage system of regulatory oversight which we have today:-

The general powers under HSWA

Notification requirements in Regulations

Inspection action by HSE

These have been the cornerstones of the UK approach to Health and Safety since 1978. In fact the United Kingdom had some 10 years' experience with such a regulatory scheme before any other European member state had established any law relating to genetic modification. This experience will be of great value in the wider arena in Europe post 1991.

The general regulatory picture in the 1980s has been that calm consideration in the light of experience with this technology worldwide has led to a relaxation of the strict systems of control originally established. In the UK this confidence came as the system of guidance expanded and as the source of that guidance changed.

By the beginning of the 1980s, the techniques of genetic manipulation were being transferred into the industrial sector. The research Council based Advisory Group became less appropriate and in 1984 GMAG was replaced by the Advisory Committee on Genetic Manipulation [Modification] (ACGM) which many of you are now familiar.

ACGM has two major rates - it has continued in the job of producing expert guidance to all users of this technology, outlining safe systems of work. In the last five years some twelve separate topics have been covered in what is one of the world's most comprehensive guides to genetic modification. ACGM has terms of reference to advise all government departments as appropriate and in this regard it is asked to advise HSE on notifications received under statutory provisions.

The ACGM based review system has been extremely successful for the last six years. The committee under chairmen of the standing, first of Sir Robert Williams and then since 1986 Professor Sir Hans Kornberg, and with a membership drawn from both sides of industry and supplemented with scientific and medical expertise has attracted much praise for its approach. Its influence has enabled HSE's oversight of the health and safety aspects of genetic modification to be developed in a way that is acceptable to users whilst at the same time ensuring that the technology is developed with the highest standards for health and safety. This has been instrumental in maintaining confidence in our regulatory scheme.

The question of confidence and of public perception was one of the factors that led to the review of the regulatory system in 1987-1988 which culminated in the passage into law of the Genetic Manipulation Regulations, 1989.

A number of factors led to the decision to update the Regulations at that time. It was felt that the definition of genetic manipulation in the 1978 Regulations had become out of date in view of a decade's progress with this technology, the Regulations only dealt with the act of construction and not the subsequent use of a modified organism either in industry or in release trials. From a legal point of view the 1978 Regulations had become technically defective.

Careful consideration was given to the option of waiting for the then draft European directives to become implemented in 1991 or 1992, but given the likely timescales involved, HSE decided it would be better to put a more solid framework of regulation down in 1989. The 1989 Regulations under which we operate our current controls recognise three activities which involve genetic manipulation: construction and modification, use, intentional introduction (release to the environment)

It is worth noting that the definitions within the 1989 Regulations are very similar to those within the two European Directives which are described below.

By bringing activities such as large scale use and release under statutory control, we replaced the successful voluntary notification frameworks already in place for such activities.

The opportunity was also taken with the new regulations to transfer ACGM guidance on risk assessment and on the establishment of local safety committees on to a legal footing. These provisions were recognised as essential elements for ensuring safety as long ago as 1976 - and the judgement of the then -Advisory Group has stood the test of time.

Since the issue of early GMAG guidance, all laboratory work on genetic modification has been categorised into four hazard groups on the basis of a risk assessment method which examines the host/vector system employed, the nature of the recombinant organism and of the product expressed. This detailed system has allowed a consistent approach to be employed by those carrying out assessment and provides users with a ranking by which the appropriate level of laboratory containment can be selected.

The risk assessment scheme has underpinned the guidance from the two advisory committees over the years and has been one factor in the safe development of this work. Given the value of this activity, HSE viewed it as appropriate for inclusion in the Regulations.

The 1989 Regulations also place into UK law a concept that has its origin in international initiatives. Since 1983 the Organisation for Economic Co-operation and Development (OECD) has maintained a programme of work under the general heading of Safety in Biotechnology. Under the chairmanship of Dr Nourish from HSE's Specialist Inspectorate, a group of national experts from the twenty four counties within OECD carried out a study that led in 1986 to the publication of the well known "blue book" - 'Recombinant DNA Safety Considerations'. Within its pages the concept of Good Industrial Large Scale Practice (GILSP) was promoted(4). OECD had set out to examine whether the risks from commercialisation of gene

technology differed from those of laboratory scale work and whether a different approach to risk assessment was needed. The task of the group was to identify scientific criteria for the safe use of recombinant organisms in industry and in the environment.

Since 1976 we have been stressing two aspects of laboratory safety. Separating workers from recombinant organisms by physical containment using the principles developed in the handling of pathogens, and the use of disabled host/vector systems to provide biological containment. It was on this latter aspect that

the OECD concentrated. By basing the industrial use of modified organisms on hosts that were especially chosen for their inability to survive outside of the fermenter or unable to compete in the environment, the level of protection to man and to the environment is greatly increased.

In the United Kingdom, such organisms are widely used following the incorporation of the criteria set out by OECD into ACGM guidance on Large Scale use. The concept of GLSP, as our guidance refers to it, states that use does not require the employment of any containment measures beyond that required for process needs.

Good Large Scale Practice is an area in which our confidence has grown and the 1989 Regulations were used as an opportunity to reduce the bureaucratic burden on industry by removing the need to pre-notify all large scale use of GMOs that had existed under the old voluntary arrangements. In the 1989 Regulations, we placed GLSP operations in the same 'low risk' classification as laboratory work at ACGM Levels 1 and 2. The Regulations simply require that provided an initial centre notification has been received, and provided that a proper risk assessment has been carried out, then GLSP work can form part of the annual retrospective return.

All non-GLSP work or laboratory scale work in ACGM Level 3 or 4 still requires to be notified in advance, along of course with all proposed releases to the environment.

The concept of 'low-risk' work that requires less vigorous regulatory control has been picked up in the European Directive on Contained Use. This significantly calls heavily on the OECD work and because of this many of the provisions of the Contained Use Directive are in line with the general approach in terms of health and safety with which the UK has become experienced(5).

## RELEASE OF RDNA ORGANISMS TO THE ENVIRONMENT

Just as technologists and regulators had come to terms with the need to deal with the safety aspects of the transfer of rDNA technology from the laboratory scale to the industrial setting, so a new and more sensitive issue was raised with regard to the introduction of modified organisms into the environment.

Sir Hans Kornberg (6) described the topic of release of rDNA organisms as generating several simultaneous debates; an essentially scientific debate in which no consensus had yet developed on whether the introduction of rDNA organism would cause harm; a regulatory debate amongst national and international agencies trying to develop the right regulatory framework in which this technology would be controlled, and a third debate in terms of public perception. Three years on, this is still the case but some progress towards the 'post-Asilomar' stage of regulatory development has occurred.

Even before the first proposal for release had been received, ACGM had recommended that all proposals to release genetically modified organisms (GMOs) should be notified to the HSE and all proposals should be reviewed on a case by case basis by the ACGM. A standing Sub-Committee, the ACGM: Planned Release Sub-Committee, later known as the Intentional Introduction Sub-Committee (ACGM: IISC), chaired by Professor John Beringer of Bristol University and constituted in the same manner as the main committee was established.

This Sub-Committee was responsible for reviewing all release proposals involving GMOs on a case by case basis. In advance of the statutory notification requirements of the 1989 Regulations, the Committee reviewed release notifications under voluntary arrangements established by the HSE.

This changed in 1989 with the passing into law of the Genetic Manipulation Regulations which require notification to the Health and Safety Executive (HSE) of the intention to release a 'genetically manipulated organism' at least 90 days in advance of work commencing.

Worldwide the number of releases of such 'novel' organisms has been rapidly increasing since the first trials in 1986. The majority of these have involved the introduction of crop plants modified to express traits such as pest or herbicide resistance, and these do not seem, as viewed from Europe, to have caused such public and media fever as that that surrounded the Pseudomonas releases in 1986 and 1987 in the USA. Nevertheless, concerns still exist and it is to provide public confidence as well as meeting genuine safety issues that regulatory authorities have issued comprehensive guidance to experimenters. There are concerns that need addressing with regards to the introduction of novel organisms whatever their type. There are examples where introduced alien species of plant, animal, insect, etc, have become established and in some cases become serious pests. Could rDNA organisms similarly fill vacant ecological niches or outcompete existing natural species? Certainly the trait of weediness in plants is a matter for serious consideration, for instance, the exchange of genetic material between modified crops and their wild weedy relatives. Characteristics such as herbicide resistance could, it is feared, become a serious problem if transferred.

In 1990, ACGM produced comprehensive new guidance on release work which contains a risk assessment procedure which addresses the following key areas; the nature of the organism and its novel genetic material; the release site and its habitat, the survival and dissemination characteristics of the released organism and safety precautions and

contingency plans. The scheme sets out a number of questions which are answered with a series of 'points to consider'. The ACGM scheme is not designed to be restricted to crop plant releases but can cope with microbial or animal species(7).

The release of rDNA organisms has been the trigger for a whole new regulatory initiative worldwide in which environmental considerations are to be at least as important as those of effects on workers or on the general public. In many respects 1990 sees the rDNA debate back in 1976. Questions are being asked but neither scientists nor regulators have sufficient experimental experience to provide reasonable answers in all circumstances. A careful step by step development of the technology will have to take place during this 'learning phase', and in this the developing regulatory framework will be of critical importance.

A second biotechnology Directive from the European Community deals with the Deliberate Release of genetically modified organisms to the environment(8). The Directive is in two parts controlling both releases for the purposes of research and development and controls on products which are or contain GMOs. Those wishing to undertake releases for research purposes will be required to notify the national competent authority in advance. An exchange of information on such proposed trial releases will operate between Member States, but the decision to give consent will remain a national one. For the foreseeable future each release will need specific individual approval, but there is provision for a simplified procedure as experience develops.

In the case of the marketing of products that are, or contain, GMOs, notification will be made to the individual national authority which, after reviewing the proposal, will circulate it to all other Member States authorities who will have to agree to the product being authorised for release. If one or more objections are received then discussions take place between authorities to a fixed timetable. Failing agreement at this stage the proposal is then to be submitted to the European Commission which will put it to an international committee acting as the final arbiter. This system is intended to produce a cross-community system of approval so that a product developed in one Member State can be licensed in all twelve.

The Deliberate Release Directive does provide exemption for those products that are subject to community-based product law which contains 'similar' provision for human and environment risk assessment. To date no such product legislation exists and for the foreseeable future the clearance system described above will operate.

The implementation of both the European Directives will require Regulations to be made under the HSW Act and compatible Regulations made under the Environmental Protection Act. Together both sets of Regulations will ensure comprehensive cover for the safety of people and the environment. The single point of entry to and exit from the system will continue. Arrangements are being made for HSE to enforce on behalf of the DoE those sections of the EP Act dealing with genetic modification ensuring a unified approach to the protection of human health and the environment.

In advance of the establishment of this new regulatory structure the Secretary of State for the Environment and the Health and Safety Commission established in April 1990, a new advisory committee, the Advisory Committee on Releases into the Environment (ACRE). This Committee subsumes the functions of the ACGM: Intentional Introduction Sub-Committee and the Department of Environment's Interim Advisory Committee on Introductions. The Committee is charged with giving advice to the HSC, HSE, Secretaries of State, Ministers and other bodies on the release into the environment of genetically modified or other novel organisms. The size and membership of the Committee reflects the broad range of expertise required to advise on matters of safety in connection with releases into the environment. It is chaired by Professor John Beringer of Bristol University and includes members nominated by the Confederation of British Industry and the Trade Union Congress, the Local Authorities Association together with a large number of experts, including environmentalists, ecologists, and microbiologists. The Committee is serviced by a joint HSE/DoE Secretariat and continues to have close liaison with the ACGM.

The release into the environment of GMOs has raised concern regarding the safety of people and the environment. Much of this concern revolves around uncertainties in the behaviour of these organisms in the environment to which they are introduced. Calls for a moratorium similar to those experienced in the early 1970s have been made. However, the consensus appears to indicate that in order to strengthen our knowledge in this area it is vital that experiments continue under a pragmatic regulatory framework which addresses both human and environmental safety.

To date controls, which have traditionally emphasised aspects of human health and safety, have been proactive in responding to the needs circumscribed by this technology. Due account must now be paid to the environment dimension. The challenge of the 1990s for regulatory authorities will be the development of a balanced and harmonised regulatory system throughout Europe which will on the one hand ensure high safety standards are observed and accidents avoided and on the other cultivate a high level of public confidence thereby creating a climate for the technology to develop.

In 1991, as we move towards full implementation of the two Directives, it is difficult to predict how they will function. Certainly industry lobby groups in Europe have expressed major reservations over the Deliberate Release Directive fearing that it will prove to be little more than a disguised moratorium on releases as sought in 1989 and 1990 by factions within the European Parliament, as a result of part C dealing with products not functioning and allowing product clearances.

These may be political points but there is unease in some quarters over the way that the process of rDNA technology is regulated by the Directive rather than the product. This implies that the risks associated with GMOs are different from those of the same organism modified by traditional strain selection - a quite opposite view to that expressed within the OECD initiative.

The aim of industry is to place its products in the market place. The new biotechnology is still only a small part of the bio-industry as a whole and it has not yet developed to a stage of self-survival. There is a danger that an overly restrictive system of control driven by public and political pressures will suffocate the baby at birth.

The UK has moved forward to recognise an increasing role for self-regulation. When genetic modification was first transferred to the industrial sector, it was felt appropriate to require the prior notification of individual proposals. This was accompanied by the issue of guidance on health surveillance which called for particular care in large-scale installations. Once industry supported the concept of GILSP, with its use of intrinsically safe organisms, it was possible to relax the more stringent requirements. As experience grows with environmental release, a similar 'fast track' clearance for 'low risk' work may also be possible.

1991 may be seen as the watershed in the development of rDNA technology. The potential benefits from the products of genetic modification are enormous, but realisation of such benefits can only come in an atmosphere of confidence that the safety issues have been properly addressed. Through the introduction of effective safety controls via a pragmatic regulatory approach such benefits can be obtained with the minimum of risk. 1991 sees a new system of regulation throughout Europe, which may come to have repercussions worldwide. The challenge will be to determine the right balance between safety needs and regulatory excess.

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