REGULATING BIOTECHNOLOGY

- *Controversy over the effect of EC Directives on the biotechnology industry.*
- *Moves to revise the regulations.*
- *How standards are entering the picture.*

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POST notes are intended to give Members an overview of issues arising from science and technology. Members can obtain further details from the PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY (extension 2840).

EC Directives on genetically modified organisms (GMOs) have been criticised as too precautionary and placing the European biotechnology industry at a competitive disadvantage. Measures to resolve this are underway, but need to avoid conflict with a major parallel exercise to set biotechnology standards.

This briefing considers how far the standard-setting process is in step with the gathering pace of biotechnology deregulation.

CHANGING ATTITUDES TO REGULATION

Techniques pioneered in the 1970s enabled scientists to transfer hereditary material (genes) between organisms in a controlled fashion. This made it possible to move genes across species barriers, creating genetically modified organisms (GMOs) that could not have arisen through natural reproduction or selective breeding. While offering great promise, scientists and regulators were also worried that the 'recombinant DNA' technology involved could be wrongly applied with unforeseen and potentially dangerous consequences.

Such concerns prompted regulatory action around the world, and in the EC ultimately led to two key Directives regulating the use of genetic modification, and the release of GMOs to the wider environment (**Box 1**). However, even while these Directives were being formulated, there was a strong scientific view that many of the hazards had been greatly overstated. Thus, by the time they were implemented in 1992, there were serious questions whether the biotechnology Directives were consistent with up-to-date scientific thinking, and increasing concern that they might adversely affect an industry which already has a European market with an estimated value of £50 billion, employing some 184,000 people.

CURRENT REGULATORY POSITION

Human health and the environment are protected from risks associated with GMOs under UK regulations which also implement the Directives in Box 1. **Research and industrial use** of GMOs in laboratories or factories are the lead responsibility for the Health and Safety Executive (HSE) under the Genetically Modified Organisms (Contained Use) Regulations 1992, while re-

Box 1 ORIGINAL BIOTECHNOLOGY DIRECTIVES

The Contained Use Directive (90/219/EC) applies to microbial GMOs and specifies various levels of containment. Two types of operation are defined;
* **type A** - small scale processes used for teaching, research, development or other non-commercial/industrial purposes
* **type B** - all other activities (e.g. large scale industrial cultures).

GMOs are also classified into two groups;
* **group 1** - organisms where the component parts are considered of low hazard. In practice this means that the microbes involved must be inherently safe, and the DNA inserted well characterised, as small as possible, relatively immobile and free from known harmful sequences.
* **group 2** - GMOs not conforming to group 1 criteria (e.g. because they are derived from pathogens).

The competent authorities in the UK are the Health and Safety Executive (HSE) and the Department of the Environment (DoE) acting jointly. Advanced notification of the intent to use premises for genetic modification for the first time is required, and this must include a description of the activity to be undertaken and a summary risk assessment. More detailed information on for instance, the GMO, the facility, containment measures, waste management, and accident and emergency plans is required for subsequent operations except for lowest risk categories

The Deliberate Release Directive (90/220/EC) requires written consent from the DoE and the HSE for any release of microbial GMOs and larger organisms such as plants. Applicants must submit a detailed assessment of the risks to human health and the environment, other information, must inform other bodies (e.g. local authorities, site owners, conservation bodies, water suppliers) of the release, and place relevant information on a public register. The Directive prescribed 89 questions covering all aspects of the release, the nature of the GMO, the processes by which it was derived and its likely affect on the environment. Applications are considered by the Advisory Committee on Releases to the Environment (ACRE), which advises the Secretary of State. Applications should normally be dealt with in 90 days, although releases for marketing purposes may take up to a further 60 days to allow comment by other Member States through the European Commission.

A third Directive (90/679/EC) concerns the health and safety implications for workers of exposure to potentially harmful **biological agents** (e.g where bacteria are used to produce chemicals, vitamins, therapeutuc drugs etc.), whether genetically modified or not. This is currently being implemented in the UK by the HSE under the Control of Substances Hazardous to Health Regulations 1988 (COSHH).

Table 1 SOME CONCLUSIONS OF THE LORDS SCIENCE AND TECHNOLOGY COMMITTEE AND THE GOVERNMENT'S RESPONSE

CONCLUSION	RESPONSE
CONTAINED USE	
Criteria for classifying organisms and activities are unscientific	Not agreed and regards most as based on a risk assessment approach. It was accepted however that organism criteria are difficult to use and imprecise, and that criteria relating to the purpose of an activity also needed attention; currently being considered by CCA.
Use of 'safe' organisms should not require advanced notification whatever the scale of use	Agreed. Case for this is being pursued within CCA.
HSE should aim to process applications for other organisms well within 90 days.	Agreed. This is already done - the target is that 80% should be processed within 30 days.
DELIBERATE RELEASE	
The Directive should be amended to allow certain activities to be subject to accelerated/ simplified notification	Goverment has long held the view that accelarated/ simpified procedures should be introduced when appropriate. Introduction of 'fast-track' and 'streamlined' procedures show that no amendment of the Directive is necessary. Further simplification can (and is) being achieved through CCA.
Questionnaire should be organism-specific	The first such annex (for crop plants) was agreed in the CCA in Feb 1994.

lease and marketing of GMOs (genetically modified plants etc.) to the wider environment is the lead responsibility of the Department of the Environment (DoE) under the Genetically Modified Organisms (Deliberate Release) Regulations 1992. Other regulations also apply (e.g. the COSHH regulations - see Box 1). The Directives were reviewed by the House of Lords Science and Technology Committee in 1993. The Committee concluded that the Directives were *'excessively precautionary'* and argued for changes to bring the Directives (and UK regulations) more in line with the latest scientific view on the risks posed by GMOs. The detailed recommendations are too numerous to be described in this overview, but followed the main underlying themes:

- Regulations should be based on the actual risks posed by the product and not driven by the fact that the process involved genetic modification.
- The Contained Use Directive sets out classification criteria for both organisms (according to hazard) and activities (according to scale and purpose). These were criticised (see **Table 1**) as fundamentally unscientific and the Government has agreed that some refinement is necessary.
- Regulations should have the strongest possible scientific basis and be better related to the risk posed. Some of the onerous, slow and cumbersome information requirements and procedures should be reduced. For instance, the deliberate release regulations required a full risk assessment based on an 89 point questionnaire (Box 1). This level of detail is now accepted as excessive and ACRE has reduced the information requirements in the light of experience and speeded up the review and authorisation processes - e.g. by introducing a **'fast-track'** (30-day) procedure for low hazard GMOs, low-risk releases and repeat releases. Further measures require changes to the directive annexes - e.g. enabling a single consent to cover multiple releases and sites (for crop plant GMOs), and formulating more organism-specific (and shorter) questionnaires.
- Experience which had shown processes to be safe should lead to their exclusion from regulation. For instance, 'safe' organisms should no longer require advance notification at larger scales.

Regulating in areas of rapidly-moving technology always presents difficulties in ensuring that specific regulations or standards do not rapidly become outdated. The biotechnology Directives attempted to ensure they could be kept up to date by assigning much of the technical detail to annexes which could be amended by a **Committee of Competent Authorities (CCA)** which could review criteria in the light of the latest scientific information and make changes. Many of the detailed points raised by the House of Lords were accepted by the Government and are being addressed via this mechanism. However, some principles seen as outdated are enshrined in the Directives themselves, and there is a growing consensus that substantial change is required[1], particularly on contained use. Urgency was lent by the 1993 EU White Paper on Growth Competitiveness and Employment which concluded that biotechnology was *"amongst the most vigorous and competitive sectors in the Community"*, and the Commisssion has now been asked by the German Presidency to rewrite the Contained Use Directive (219) in time for December's Council Meeting. Current drafts adopt a more flexible risk-assessment based approach to replace the current classifications for organisms and processes, and should also simplify notification and consent requirements.

This shift in regulatory attitudes (so-called 'deregulation') has concerned environmental groups, which would particularly oppose any significant weakening (as opposed to streamlining already underway) of the deliberate release regulations[2]. They argue that industry has exaggerated the effects of current regulations on competitiveness, and also point out that such moves

1. The regulations have also been examined by the DTI Task Force on deregulation and by the Industry's Special Advisory Group on Biotechnology (SAGB) which broadly supported the Lords' conclusions.

2. Environmental groups such as the Green Alliance and industry via SAGB have both published their respective views on the risks of releasing GMOs to the environment.

Box 2 THE CEN PROCEDURES FOR SETTING STANDARDS

The 54 standards identified by CEN and agreed by the Commission were grouped under the four headings shown in the Table below. Each work area is delegated to a project group, which reports back to one of the 4 main Working Groups. Groups 1,2 and 4 are mainly concerned with contained use; Working Group 3 with deliberate release.

Once a project group has produced a first draft of a document, it is discussed by the appropriate Working Group, and if approved, referred to a central CEN Technical Committee (TC 233) consisting of around 40 members representing all the national standards bodies. Approved drafts are then forwarded to each of the national standards bodies for a formal (qualified majority) vote, which will determine whether or not a proposed standard is adopted. UK representation is through the British Standards Institution (BSI), which has set up a Biotechnology Committee (CIC 58) specifically for this purpose. Votes are decided after a consultation process involving one of four 'shadow' panels (one for each of the CEN Working Groups), consisting of representatives from all interested UK parties (e.g. industry, regulators, BioIndustry Association).

Table Areas Covered by CEN Working Groups

Group	No. of Stds	Example of Standard
1. Laboratories for research, development and analysis	10	guidelines on containment
2. Large scale process and products	7	plant building
3. Standards relating to applications of GMOs in the environment	11	how to identify GMOs
4. Equipment	24	performance crieria for valves, joints,fermenters etc.

could be counterproductive if it undermined public confidence in the safety of GMOs. Nevertheless, the pace of change is already significant, and against this background, the parallel activity of setting 54 standards to implement the original directives assumes some importance.

EUROPEAN BIOTECH STANDARDS

Although the Directives' primary means of implementation is via the laws of Member States, they include many terms (e.g. 'minimise', 'prevent') which generate a need for interpretive standards if measures are to be uniform across the EU. The European Commission thus decided in 1992 to commission the European Committee for Standardisation (CEN)[3] to produce 54 detailed standards, guidelines or reports.

The CEN standards setting process is very involved (Box 2) and slow, and the first detailed drafts are only expected to emerge in autumn 1994. Overall, the intention is to have implemented the majority of the new standards by 1997. When agreed, a European standard will replace a national equivalent, such as those put out by the British Standards Institution (BSI), though they will not replace the guidance of official bodies such as the Advisory Committee for Genetic Manipulation (ACGM) or ACRE.

ISSUES

The Need for Standards

The way in which the Directives have been implemented in the Member States varies considerably. Some (e.g. Germany and Denmark) have introduced a stricter regime than required under the Directives, while others (including France and Belgium) have produced less exacting regimes by blending the Directives' requirements into pre-existing national regulations. In requesting CEN to develop 54 standards, the Commission had in mind that they would help implement the directives more uniformly across the EU[4]. However, in the actual request to CEN, the Commission placed an explicit objective on CEN to "*improve competitiveness in community and external markets*". How compatible are these separate objectives?

The UK and EU biotechnology industry is operating in a market in which US and Japanese companies are very active under their own regulatory regimes, and thus the EU regulatory regime is an important factor in the future development of the European industry. As far as competitiveness in external markets is concerned, the Lords' enquiry, SAGB and the DTI Derugulaion Task Force all concluded that EU regulations were already too strict and placed UK and EU companies at a competitive disadvantage relative to Japanese and American companies operating in a more flexible system.

While there is some sympathy in industry for encouraging Europe-wide standards as a general principle to encourage European harmonisation, the need for 54 standards in biotechnology has been questioned, particularly since it contrasts starkly with the level of activity in other sectors[5]. The substantial changes to the directives in hand also raise the question of whether the rationale for such an extensive and separate standards exercise is affected. Changing the directives will affect the need for and nature of the standards desired, and many observers are concerned that the standards process will have the effect of institutionalising outdated principles and approaches, thus complicating or even negating the current efforts to improve the competitiveness of the European biotechnology industry.

For instance, some CEN Work Groups are examining

3.The Centre European pour Normalisation is an organisation formed in the early 1980s consisting of 18 national standards bodies within Europe (including EU and EFTA states).

4. Although standards are seen as a means of imposing a 'level playing field' throughout Europe, it is not clear that they would have this effect in practice. Although CEN standards do override national ones, they have no legal status, since neither Directive refers to them, and their final impact will depend on how vigorously each Country decides to encourage or require their use.

5. For instance in the food area, only one standard is underway. Most other Technical Committees also deal with only a few standards at a time.

the classification of organisms or the levels of containment appropriate in different circumstances - matters at the heart of the Directives' scope and the focus of current proposed revisions to the Directives. In such areas it is essential that the respective roles of teh Directive and CEN be clearly defined if the potential for confusion, duplication or even conflict is to be avoided. Other subjects for standards are less questionable in principle but raise concerns that they may reduce rather than increase the flexibility of the biotechnology regulations under amendment.

Making the system work

Despite the misgivings above, many see the standard setting process as beyond recall and groups such as SAGB see the main priority as ensuring the system delivers sensible standards (i.e. relecting current UK regulatory attitudes) in only those areas where they are needed. Hence, the two main issues concern UK representation, and the scope of the process itself.

Representation. Although complex (Box 2), there are a number of carefully constructed consultative steps and decision mechanisms that should ensure standards receive the proper scrutiny by each country's expert bodies and industry before being adopted. Countries which encourage their relevant institutions to participate fully will, however, have the greatest influence on the outcome. The UK is currently well represented on the various CEN committees and working groups, providing some 15 of the 54 project leaders. The BSI is also very active and, in conjunction with the Bio-Industries Association (BIA), has set up shadow groups in each of the main project areas to aid the consultation process within the UK.

Nevertheless, concerns have been expressed about the level of industry participation in the standard setting process, and about the additional burden (in terms of costs and time) placed upon participants from academia. Historically, UK industry has been noticeably more reluctant to get involved than its competitors in Switzerland, Germany and France, although a series of 'leaked' drafts from one of the Working Groups has done much to raise industrial interest. Nevertheless, further measures to encourage industrial participation are still seen as necessary, despite the involvement of industry in fora such as BIGRAG (Biotechnology Industry Government Regulatory Advisory Group) and the DTI Deregulation Task Force, both of which are currently examining the CEN standards. In parallel, some argue that DTI should help academic experts to participate by providing additional financial support, since it is on them that much of the burden of drafting the standards, attending meetings etc. actually falls. The Commission has made funds (ECU 1.5M) available for the standards setting process, but this is all allocated to the secretariats of the various working groups - none is available to cover expenses incurred by project leaders and other experts. While companies are usually happy to fund industry representatives, academics find it more difficult to secure funding. DTI policy at present is to fund only one UK representative to attend Working Group meetings, and many see this as effectively limiting participation in the process by academic experts.

Scope. There is consensus that in a fast-moving area such as biotechnology, standards are the most appropriate way of handling technical details, since they are easier to amend (e.g. in the light of technological advance) than legislation. However, as described above, the current process is now widely viewed as having lost touch with prevailing regulatory attitudes to the extent that many of the 54 areas are not regarded as suitable subjects for standards at all. Only in Working Group 4 (and part of 1) - which cover technical specifications for equipment - are standards seen to be appropriate, while many of the areas covered in Working Groups 1, 2 and 3 (Box 2) are seen as being more suitable subjects for guidance, best practice notes etc.

There are two basic options for redirecting the standards exercise. One is to suspend the process until the legislative framework is finalised, after which the Commission could review and restrict the scope of the standards to those which are appropriate to biotechnology and seen as helpful by the industry. The second would be to proceed to develop standards which are sufficiently flexible to accomodate changes resulting from amendments to the Directives. For instance, in those areas where standards are seen to be inappropriate, Working Groups are likely to produce drafts that more closely resemble guidance on best practice than standards. While the value of many of the 'standards', guidance etc. emerging from this pragmatic approach can be questioned, it may nevertheless ensure that the potential adverse effects on competitiveness are minimised.

If this approach is taken however, there are two dangers. Firstly, some of the subject areas (e.g. microbiological safety cabinets) have applications outside biotechnology. If current BSI standards were to be replaced by a new and less precise CEN standard, this could have implications for safety in more hazardous (non-biotechnology) applications for such equipment. Secondly, there is the possibility that CEN standards could assume greater significance than currently envisaged if, as some believe, future amendments to the Directives formally link the legislation to the standards, giving them the legal basis they currently lack. The UK opposes any such move, but at least one country (Belgium) is openly supportive of linkage, and the issue is likely to be a subject for continuing debate within the EU.