Journal of Industrial Microbiology, 11 (1993) 209–215

Published by Elsevier

SIM 00474

Comparative analysis of current US and EC biosafety regulations and their impact on the industry

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SUMMARY

On July 18, 1991, the US National Institutes of Health added a section entitled 'Good Large-Scale Practice' (GLSP) to Appendix K of the *Guidelines for Research Involving Recombinant DNA Molecules*. Highlights of this section include the requirement for: (i) a health and safety program; (ii) well-trained personnel; (iii) facilities, clothing and practices appropriate to the risk of exposure; (iv) discharges to air, water and soil that must be done in accordance with environmental regulations; (v) aerosol generation that must be kept to a minimum so that employee health is not adversely affected; and (vi) a spill control plan. This complements the blueprint for regulation of biotechnology in the US (Coordinated Framework for Regulation of Biotechnology), in which the jurisdiction of each federal agency is established. Activities in Europe at this time included the adoption of three directives by the European Economic Community: "on the protection of workers from risks related to exposure to biological agents at work", "on the contained use of genetically modified organisms", and "on the deliberate release of genetically modified organisms". The relationship of these new guidelines and regulations to existing practices and their potential impact on future activities are discussed.

EVOLUTION OF LARGE-SCALE CONTAINMENT GUIDELINES IN THE UNITED STATES

It has been nearly two decades since a group of concerned scientists met at Asilomar, CA to consider the safety of gene cloning and its potential adverse effects on the environment [24]. This gathering led to the first version of the US National Institutes of Health (NIH) *Guidelines for Research Involving Recombinant DNA Molecules* (Guidelines) [15], which was published in 1976 to provide a framework for conducting genetic engineering research in a manner that protects employees from infection and prevents adverse impact on the environment. This first set of guidelines was both cautious and conservative in approach, prohibiting all large-scale (> 10 liters) cultivation of recombinant DNA-containing organisms. It was not until 3 years later that the Recombinant DNA Advisory Committee (RAC) agreed to begin reviewing large-scale protocols, and only after it was determined in advance that the application was expected to result in a positive benefit for humankind.

By 1979, the perceived perils of recombinant DNA (rDNA) had failed to materialize and RAC began to relax its containment criteria. They created a Large-Scale Review Working Group to develop guidelines for the large-scale cultivation of rDNA-containing organisms. The efforts of this group led to the publication of "Physical Containment for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules" in April, 1980 [16], which described three levels of large-scale physical containment – Biosafety Level 1-Large Scale (BL1-LS, originally termed P1-LS), Biosafety Level 2-Large Scale (BL2-LS, originally termed P2-LS) and Biosafety Level 3-Large Scale (BL3-LS, originally termed P3-LS). In addition, they delegated responsibility for review of large-scale uses to the local Institutional Biosafety Committee (IBC). Prior to this, all such applications had to be approved by the NIH-RAC prior to initiation.

The evolution of the large scale guidelines continued with their incorporation into the Guidelines as Appendix K in 1983. This was the result of favorable action on a proposal from Schering Corporation, seeking to make the Guidelines a comprehensive reference document for IBC members by combining the small and large scale recommendations in one place.

With the passing of time came a better understanding of the hazards of rDNA-containing organisms and a concomitant increase in the number and volume of organisms being handled in industry. Many began to question why containment for low hazard rDNA-containing organisms was more strict than that for the parental strain when the DNA insert bestowed neither an increase in pathogenic-

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ity nor enhanced its ability to persist in the environment. Physical containment conditions described in BL1-LS seemed overly restrictive in this instance, which resulted in debate concerning the acceptability of BL1-LS as the minimal requirements for the large-scale cultivation of rDNA-containing organisms. One significant result appeared in 1986 when the European-based Organisation for Economic Cooperation and Development (OECD) published a report entitled, *Recombinant DNA Safety Considerations* [13], in which they described appropriate physical containment practices for rDNA-containing organisms. The term "Good Industrial Large-Scale Practice" (GILSP) was introduced as a level of containment appropriate for organisms meeting the following criteria:
(a) The host organism should be non-pathogenic, should not contain adventitious agents and should have an extended history of safe industrial use or have built-in environmental limitations that permit optimum growth in the industrial setting but limited survival without adverse consequences in the environment.
(b) The rDNA-engineered organism should be non-pathogenic, should be as safe in the industrial setting as the host organism, and without adverse consequences in the environment.
(c) The vector/insert should be well characterized and free from known harmful sequences; should be limited in size as much as possible to the DNA required to perform the intended function; should not increase the stability of the construct in the environment unless that is a requirement of the intended function; should be poorly mobilizable; and should not transfer any resistance markers to the microorganisms not known to acquire them naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.

Also in 1986, the United States Office of Science and Technology Policy (OSTP) of the Executive Office of the President accepted the concept of GILSP as national policy in its *Coordinated Framework for the Regulation of Biotechnology* [20].

"The appropriate large-scale containment requirements for many low-risk DNA-derived microorganisms will be no greater than those appropriate for the unmodified parental organisms... The approach of the comprehensive framework contained in the notice takes into account *inter alia* the broad goals described by an Ad Hoc Group of Government Experts convened by OECD in their report, "Recombinant DNA Safety Considerations, Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques"... The report includes the following concepts:... The vast majority of industrial rDNA large-scale applications will use organisms of intrinsically low risk which warrant only minimal containment, Good Industrial Large-Scale Practice (GILSP)... The large-scale industrial application of rDNA technology should wherever possible utilize microorganisms that are intrinsically of low risk. Such microorganisms can be handled under conditions of Good Industrial Large-Scale Practice (GILSP)." [21].

In 1988, the RAC and NIH Director approved a modification of the Guidelines that reads:

"For large-scale fermentation experiments involving non-pathogenic and non-toxigenic recombinant strains having an extended history of safe industrial use, the IBC may set large-scale containment conditions at those appropriate for the host organism unmodified by recombinant DNA techniques and consistent with good industrial large-scale practices." [17]

While the NIH recognized the appropriateness of GILSP for non-pathogenic and non-toxigenic organisms, Appendix K did not contain recommendations for suitable facilities and practices. Likewise, while the OECD report was specific in establishing the criteria for qualifying an organism as GILSP, it did not include recommendations for facilities and practices appropriate for this level of containment. This void in the guidelines was recognized by representatives of the Pharmaceutical Manufacturers Association (PMA) and Industrial Biotechnology Association (IBA), whose Bioprocessing Committee initiated a project to specify appropriate criteria for the GILSP level of containment. A rDNA-containing microorganism that meets the OECD criteria for GILSP is no more hazardous than those agents that have been used for decades to manufacture such products as antibiotics, enzymes, yogurt, beer and wine. Accordingly, facilities and practices to achieve GILSP should be consistent with those used for traditional fermentations. On June 28, 1990, the IBA-PMA Bioprocessing Committee presented its recommendations for the GILSP level of containment to the NIH-RAC for consideration. A significant portion of this document was based on work completed in Europe [11]. A little more than a year later, on July 18, 1991, the NIH Director issued a notice [18] modifying the guidelines to include a new level of physical containment called Good Large-Scale Practice (GLSP). Similar to the OECD version from which it is derived, GLSP is a "level of physical containment (that) is recommended for large-scale research or production involving viable, non-pathogenic, and non-toxigenic recombinant strains derived from host organisms that have an extended history of safe large-scale use. Likewise, ... (it) is recommended for organisms such as those included in Appendix C that have built-in environmental limitations that permit optimum growth in the large-scale setting but limited survival without adverse consequences in the environment" [18]. Highlights of this section of Appendix K include requirements for:
1. Formulating and implementing institutional codes of practices to assure adequate control of health and safety matters.
2. Writing instructions and training personnel to assure

that cultures are handled prudently and the workplace is kept clean and orderly.
3. Providing facilities, clothing, equipment and practices that are appropriate for the risk of exposure to viable organisms.
4. Assuring that environmental discharges are handled in accordance with applicable governmental environmental regulations.
5. Controlling aerosols in a manner that maintains employee exposure to viable organisms at a level that does not adversely affect the health and safety of employees.
6. Including provisions for handling spills in the facility's emergency response plan.
A comparison of GLSP with BL1-LS yields a number of differences that are summarized in Table 1.

The implementation of GLSP, particularly those elements relaxing the requirements for filtration of exhaust air, have the potential for saving the fermentation industry millions of dollars in capital investment. This comes without increasing the risk of injury to employees or the public or contamination of the environment.

REGULATION OF BIOTECHNOLOGY IN THE EUROPEAN COMMUNITIES

The current scheme for the regulation of biotechnology in Europe is rooted in the 1987 adoption of the Single Europe Act (Act) by the Commission of European Communities [14]. Through this legislation, the 12 member countries have committed to the harmonization of the social dimension: employees' rights, living standards and safety at work. The goal is to develop a single European market that removes all physical, technical and fiscal barriers to the free movement of people.

According to the Act, member states are to encourage improvements in the working environment regarding the health and safety of workers through the development of national laws corresponding to EC directives. These directives require consultation with the workforce (referred to as "balanced participation") and the provision of information regarding risks. The test of the Act holds employee health and safety paramount when it states: "Safety, hygiene and health at work is an objective which should not be subordinated to purely economic considerations" [14]. If measures are inadequate, work can be suspended and the employee can appeal to an inspector. This approach is similar to contacts made by employees in the US with the Occupational Safety and Health Administration (OSHA). With this Act, Europe embarked on a holistic approach to worker health and safety and also developed minimal health and safety standards for manufacturing, including testing and certification, to assure safety, quality and efficacy of products.

The Act has increased the speed with which general safety directives are developed well beyond that previously seen for specific hazards such as asbestos and noise. In 1989, the EC adopted the Framework Directive [5] establishing general guidelines to prevent exposure to occupational risks. The Framework Directive serves as the core for the harmonization of health and safety standards to be accomplished by December, 1992. Of approximately 282 Directives issued to date, 70 laws have been written in the social area, e.g., collective bargaining and the free movement of labor. A key element of the Framework Directive is Article 6(4), which makes those who share a

TABLE 1

Comparison of GLSP and BL1-LS

Criterion	GLSP	BL1-LS
1. Culture fluids are not removed from a system until all organisms are inactivated.	not required	required
2. Viable organisms should be handled in a system that physically separates the process from the external environment (closed system or other primary containment).	not required	required
3. Inactivation of waste solutions and materials with respect to their biohazard potential.	per environmental regulations	required
4. Control of aerosols to prevent or minimize release of organisms during sampling, addition of materials, transfer of cells, and removal of material, products and effluents from a system.	minimize using procedural controls	minimize using engineering controls
5. Treatment of exhaust gases from a closed system to minimize or prevent release of viable organisms.	not required	required
6. Closed system that has contained viable organisms not to be opened until sterilized by a validated procedure.	not required	required

workplace responsible for coordinating their actions in protecting and preventing occupational risks and for informing one another and other workers or the worker's representative of these risks.

The Framework Directive sets out general principles for developing directives on occupational issues, such as personal protective equipment (PPE) and video display terminals (VDTs), rather than on specific hazards. It closely resembles the 1974 Health and Safety at Work Act of the UK that provides a legal framework within which specific areas are covered by various regulations. It differs from the approach legislated in the US by the Occupational Safety and Health Act of 1970 (OSH Act) that has led to the promulgation of specific standards on hazards such as asbestos, formaldehyde, etc. It is only in recent years that OSHA has chosen to deal, upon occasion, with broader issues, such as chemical hazard communication and PPE. The EC PPE directive permits the use of PPE only if the risk cannot be eliminated. Safer alternatives, such as the use of a different process or a change in the working environment, must be pursued before PPE is required. Employers must carry out a risk assessment and give their reasons for selecting certain PPE.

European standards are performance standards that offer the user a flexible method of compliance. OSHA standards, on the other hand, have traditionally established minimum requirements for compliance, which often have resulted in employers doing the very least they have to in order to comply. In recent years there have been signs of a more flexible, performance-based approach at OSHA with the new bloodborne pathogen standard [19] being a good example.

Each EC member state is required to adopt new national laws that comply with each of the issue-specific directives. A parallel to this approach can be found in the US where some states have decided to develop their own health and safety programs. The state program must be as stringent as the federal version and comply with all provisions of the OSH Act and individual standards promulgated by OSHA. In implementing these new European laws, some countries, such as the UK, plan to continue to issue them under the Health and Safety at Work Act rather than introduce a radical change in their existing laws.

The EC Directives are intended to remove technical barriers (Article 100A) and to provide for equipment and type approval of PPE, machines, safety devices, etc. Individual country certifications, e.g., UK:BS, France:AFNOR, Germany:DIN, etc., will remain in effect until the Committee for European Normalization (CEN) and the CENELEC for electricity have developed EC minimum standards. The EC aims to formulate directives based upon current international standards wherever possible. Exposure limits will be "reasonably practical" to eliminate or reduce the risk of exposure to hazardous chemicals to as low a level as possible. This is similar to the ALARA (as low as reasonably achievable) concept used in the US for radioactive isotope handling.

Some of the daughter safety directives developed under the Framework Directive include three that impact upon biotechnology and biosafety. They are a directive on the protection of workers against the risk of exposure to biological agents at work [8] and two directives covering the contained use and deliberate release of genetically modified organisms [6–7].

The Council directive on the protection of workers from the risks related to exposure to biological agents at work was adopted for the health and security of workers. Biological agents are defined as microorganisms, including recombinant organisms, cellular cultures and human endoparasites. Levels of confinement (i.e., technical measures that must be applied to ensure the most efficient barrier between the agent and the worker) are described in the text of the directive. These barriers and special measures are related to the level of risk of the agent, the degree of the intrinsic danger as described in a classification scheme comprised of four groups, and the type of work being done. There are separate compilations of measures for research and for industrial procedures, for animals used in research and for certain medical services and diagnostic labs. The directive covers all work with biological agents and advocates medical surveillance to evaluate the general state of the potentially exposed worker. A recent draft amendment [9] includes a list of agents classified for use in this directive along with some interesting points to consider in their application.

The two directives on the use of genetically modified organisms (GMOs) were adopted in April, 1990. They impose environmental controls on experimental and commercial activities that use GMOs, e.g., genetically modified microorganisms, plants and animals. The contained use directive covers GMOs handled in physically, chemically or biologically contained environments. This directive sets minimum conditions for containment and upkeep based upon the classification of the GMOs into two groups. Group I is for non-pathogenic organisms with poorly mobilizable genetic elements and a proven history of characteristics that provide for limited survivability and limited ability to replicate in the external environment. Guidelines for classification into group I were revised dramatically in 1991 [3] to request significantly more detailed information on the parental organism, vector, inserts, the recipient and the genetically modified organism that results from this process. Group II consists of all other GMOs. Specific containment measures for group II are based upon the biological properties of the microorganism

and the characteristics of the activity or operation in which it is used.

Notification of a decision to commence an activity under the contained use directive must be made to a competent authority in the member state and must include an emergency plan and corrective measures to be taken in the event of an accident. Member states are required to file annual reports of contained use activities under their jurisdiction to the Commission.

The deliberate release directive is similar but extends the scope of the GMOs covered to those 'placed on the market as, or in, a product'. Deliberate release activities must be approved in advance of any actual release. Notification must include complete technical data as described in Annex II of this directive. A risk assessment of known or potential environmental impact is also required. Releases are allowed only under conditions of human and environmental safety that are as high as reasonably practical. During the review process, the Commission forwards the application to the member states for evaluation. If no objections are raised within 60 days, the Commission provides written notification to proceed. If there are objections, a qualified majority decision is made. The Organisation for Economic Cooperation and Development (OECD) consensus reached in 1986 [13] has been adopted as a case-by-case approach to the evaluation and approval of releases. A national approval will probably be required for experimental releases. Product release requires approval from the EC and the entire community. However, once done, no additional notification is required.

A recent announcement from the EC Committee on Standards and Technical Regulations noted that in terms of volume of production, most industrial processes do not use GMOs. Those agents that are used are class I agents directed to produce pharmaceuticals, biodegradable plastics, bread, beer or food enzymes. In most cases, there is no scientific or industrial need to use pathogenic organisms. One possible exception is when the pathogenic trait is needed, such as during the production of vaccines or the testing of effectiveness of pharmaceuticals.

UNITED STATES REGULATION OF BIOTECHNOLOGY

In the US, the Coordinated Framework for Regulation of Biotechnology was announced as national policy in June, 1986 [20]. This document continues to be the federal government's blueprint for the allocation of oversight responsibilities for biotechnology products. It lists the federal agencies from which approval must be obtained for commercial products and the research jurisdictions of each department. Responsibility for oversight of biotechnology is based on use, just as for traditional products. Existing statutes are viewed as being sufficient to establish jurisdiction over both research and products, and to assure reasonable safeguards for the public and the environment. To facilitate an expeditious review, the Coordinated Framework promises that every effort will be made to assure that regulatory responsibility for a product will be with a single agency. Foods, food additives, human drugs, biologics and devices, and animal drugs are reviewed or licensed by the Food and Drug Administration (FDA). Food products made from domestic livestock and poultry are under the US Department of Agriculture's (USDA) Food Safety Inspection Service (FSIS). Animal biologics are reviewed by the Animal and Plant Health Inspection Service (APHIS), which also reviews plants, seeds, plant pests, animal pathogens and regulated articles, i.e., certain genetically engineered organisms containing genetic material from a plant pest. An APHIS permit is required prior to movement or release of a plant pest or animal pathogen.

"Other contained uses" (i.e., cultivation in a closed system) of intergeneric combinations (i.e., deliberately formed microorganisms that contain genetic material from dissimilar source organisms) are covered by the Toxic Substances Control Act (TSCA) and subject to the Environmental Protection Agency (EPA) Pre-Manufacture Notice (PMN) requirement. EPA also reviews microbial pesticides, with APHIS being involved when the pesticide is also a plant pest, animal pathogen or regulated article requiring a permit.

The category "other uses (microorganisms)" includes applications involving release into the environment. For these, jurisdiction depends on the characteristics of the organism as well as its use. Intergeneric combination microorganisms are to be reported to EPA under PMN requirements, with APHIS involvement in cases where the microorganism is also a regulated article requiring a permit.

An additional category of oversight is "intrageneric combinations", which encompasses those microorganisms formed by genetic engineering through other than intergeneric combinations. APHIS has jurisdiction over such organisms when the source organism is a pathogen and the microorganism is used for agricultural purposes. If it is used for non-agricultural purposes, it is within the realm of EPA with APHIS involvement in cases where the microorganism is also a regulated article requiring a permit. Intrageneric combinations with no pathogenic source organisms are regulated by EPA, although EPA will probably only require an informational report.

The Coordinated Framework left unanswered the question of whether federal government oversight should be product or process based. Under the former approach,

no special emphasis would be placed on the method that was used to create a product. Review of the results of genetic engineering would be carried out in the same manner as reviews for traditional products. In a process-based approach, biotechnology products would be reviewed with special emphasis on the genetic engineering methods that resulted in the product. This was recently resolved by the Office of Science and Technology Policy, which stated that federal government oversight would be "product" based [22].

From the employee perspective, OSHA did not find a need to develop further regulations for biotechnology. Specific standards, such as those for PPE, are already available and guidelines for other aspects of health and safety can be enforced under the general duty clause.

GLOBAL CONSIDERATIONS: REGULATIONS AND STANDARDS

There has been some attempt at harmonization between the US federal agencies and their European Community counterparts. For example, the Department of Transportation (DOT) has accepted the United Nations (UN) and International Air Transport Association (IATA) requirements for transportation of hazardous materials and the FDA is working with its counterpart in the EC.

As the US struggles to compete in the EC market, the issue of European standards presents a formidable challenge. The EC may require more stringent testing than we currently do to obtain the prized CE mark. This becomes particularly frustrating when one considers that the US can voice opinions in the standardization process but cannot vote. Ultimately, this process could result in European standards becoming global standards, which we will have to meet. The EC has already asked the CEN to establish standards on: laboratory categorization; waste handling, inactivation and testing; codes of good practice for laboratory operations; guidelines for animal containment in experiments; definition of equipment needed in microbiological laboratories according to hazard; codes of practice for large-scale process and production; standards required for quality control procedures; standards related to modified organisms for plant and soil application and standards relating to microorganisms that are human, plant and animal pathogens. The standards will define in concrete terms the technical specifications, codes, methods of analysis and lists of organisms needed to complement legislation. Unfortunately, they also will undoubtedly take some of the flexibility out of compliance with the directives. One benefit is that with the announcement of EC standards development, the member countries cannot introduce their own standards in these areas.

CONCLUSION

Since the hazards of rDNA technology were first discussed nearly two decades ago, the issue of regulation of this science has remained ever present. To date, the most successful approach has been the use of the NIH Guidelines – a document that was initially conservative and cautious but which has become more lenient and less restrictive with time as the perceived hazards of rDNA are discovered to be unfounded. While many would agree that regulation of biotechnology in some form is necessary, most feel that the lack of problems associated with rDNA technology thus far does not support the extensive amount of information required for GMOs in the EC. To prevent unnecessary crippling of this fledgling industry, regulation must be based on reality rather than on perception. Biosafety guidelines have been developed for the containment of pathogens and are effective regardless of whether or not the pathogen is a GMO. Once a realistic assessment is conducted for the relative risk of the agent, the activity and the host, appropriate levels of physical and biological containment can be prescribed. Such facts must be incorporated into current and future regulations to assure that they reflect the actual risks rather than the public perception of risk.

REFERENCES

1 Ballard, J. 1992. Safety in the New Europe. Occupational Hazards. March, 1992: 65–67.

2 Brown, K. 1992. Regulatory Environment Rapidly Evolves in European Economic Community. Genetic Engineering News. April, 1992: 9–10.

3 Commission of the European Communities. 1991. Commission Decision of 29 July 1991 concerning the guidelines for classification referred to in Article 4 of Directive 90/219/EEC. 91/448/EEC. Official Journal of the European Communities. No. L 239: 23–26.

4 Commission of the European Communities. 1991. Commission Directive of 1 March 1991 adapting to technical progress for the twelfth time Council Directive 67/548/EEC of the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. 91/325/EEC. Official Journal of the European Communities. No. L 180: 1–78.

5 Council of the European Communities. 1989. Council Directive of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. 89/391/EEC. Official Journal of the European Communities. No. L 183: 1.

6 Council of the European Communities. 1990. Council Directive of 23 April 1990 on the contained use of genetically modified micro-organisms. 90/219/EEC. Official Journal of the European Communities. No. L 117: 1–14.

7 Council of the European Communities. 1990. Council Direc-

tive of 23 April 1990 on the deliberate release into the environment of genetically modified organisms. 90/220/EEC. Official Journal of the European Communities. No. L 117: 15–27.

8 Council of the European Communities. 1990. Council Directive of 26 November 1990 on the protection of workers from risks related to exposure to biological agents at work. 90/679/EEC. Official Journal of the European Communities. No. L 374: 1–12.

9 Council of the European Communities. 1991. Draft proposal for a Council Directive amending Directive 90/679/EEC on the protection of workers from risks related to exposure to biological agents at work. Doc. No. 4903 EN.

10 FCCSET Committee on Life Sciences and Health. 1992. Biotechnology for the 21st Century. Superintendent of Documents, ISBN 0-16-036101-X, Washington, DC.

11 Frommer, W., et al. 1989. Safe Biotechnology. III. Safety Precautions. Appl. Microbiol. Biotechnol. 30: 541–552.

12 Mackay, D. EC 1992 and the Construction Products Directive. ASTM Standardization News. February, 1992: 48–52.

13 Organization for Economic Cooperation and Development. 1986. Recombinant DNA Safety Considerations, Safety Considerations for industrial, agricultural and environmental applications of organisms derived by recombinant DNA techniques.

14 Parliament of the European Communities. 1987. Treaty Establishing a Single Council and a Single Commission of the European Communities. Official Journal of the European Communities. No. L 152: 2.

15 United States National Institutes of Health. 1976. Guidelines for Research Involving Recombinant DNA Molecules. In: Federal Register, Vol. 41, No. 131.

16 United States National Institutes of Health. 1980. Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules. In: Federal Register, Vol. 45: 24968.

17 United States National Institutes of Health. 1988. Guidelines for Research Involving Recombinant DNA Molecules. In: Federal Register, Vol. 53: 43411.

18 United States National Institutes of Health. 1991. Guidelines for Research Involving Recombinant DNA Molecules. In: Federal Register, Vol. 56: 33178.

19 United States Occupational Safety and Health Administration. 1991. Occupational Exposure to Bloodborne Pathogens. Title 29. Code of Federal Regulations, Part 1910.1030.

20 United States Office of Science and Technology Policy. 1986. Coordinated Framework for Regulation of Biotechnology. In: Federal Register, Vol. 51: 23304.

21 United States Office of Science and Technology Policy. 1986. Coordinated Framework for Regulation of Biotechnology. In: Federal Register, Vol. 51: 23308.

22 United States Office of Science and Technology Policy. 1992. Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment. In: Federal Register, Vol. 57: 6753.

23 Vogel, C. 1992. EC '92: Here Comes a New Set of Rules. Safety Health 145: 32–36.

24 Watson, J.D. and J. Tooze. 1981. The DNA Story: A Documentary History of Gene Cloning. W.H. Freeman and Company, San Francisco.