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Biotechnology Regulation in the Health Sector

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1. Purpose and scope of the report

The main thrust of this report is directed to existing and proposed regulation of health products emerging from biotechnological innovation in a range of countries. The report will also address the debate that has surrounded policy making in this field, and consider future regulatory needs. However, many other biotechnological innovations, whatever their field of use, can have effects on human health, and since the issues overlap these will also receive some attention.

A degree of caution is called for in examining these trends and needs. Experience in the long-established field of drug regulation shows that perceptions of need and of risk change progressively (and sometimes abruptly) as science develops and experience is gained. Whatever policies may be devised at present to serve the community's needs to 2030, they are likely to require substantial revision as time passes.

Finally, one should note at this point that while the term "regulation" tends to imply a system of legally binding rules backed by control, inspection and sanctions, this use of the term may be too narrow. The community sometimes chooses simply to develop a consensus on desirable standards, trusting in whole or in part in a system of voluntary regulation to ensure that these standards are respected in practice.[21] Both official and voluntary regimens, which often complement one another, need to be considered in the present discussion.

2. Biotechnology relating to health: definition of the field

Any attempt to define "health biotechnology" adequately soon runs into difficulties because the field is so immense (and growing) and its boundaries so poorly defined. Certain innovations introduced into medicine and the health field during the last two decades could be considered as "biotechnological" (see examples in Section 4 below), but in all likelihood they represent only a modest beginning.[22] It is entirely true, as the OECD Scenario Report notes, that biotechnological processes have to date contributed to the continuation of the established process of drug development rather than complementing it with entirely new approaches,23 but a distinct shift is now taking place. Small spin-off companies on both sides of the Atlantic (and elsewhere) are opening some novel biotechnological doors to possible new forms of prophylaxis and treatment; the major corporations, which have suffered a dramatic fall in their own innovative output since 1990,[24] have increasingly sought to benefit from this activity, either by licensing agreements or by outright acquisition.

Viewed more broadly, the scope of biotechnological exploration is widening dramatically. A draft OECD report that the present writer had sight in October 2007,[25] which specifically excluded traditional biotechnological techniques (such as grafting and selective breeding), nevertheless listed at various points some 150 very diverse areas that would need to be considered when defining policies. That section of the report must be cited here for purposes of discussion since it illustrates, much better than any more compact definition, the problem that one faces when seeking to examine regulatory policies for this field.

[21] See for example guidelines on Clinical Trials, Drug Promotion and other matters issued by the Association of British Pharmaceutical Industry.
[22] OECD Health Scenarios, Third Report (Draft) 2007 at page 2.
[23] OECD Health Scenarios, Third Report (Draft) 2007 at page 4.
[24] See evidence reviewed by Dukes MNG (2005): The Law and Ethics of the Pharmaceutical Industry. Elsevier, Amsterdam and New York, at pp. 235-260.
[25] *Definition of Biotechnology for the Bioeconomy to 2030.* Confidential Draft, OECD, June 2007.

Slightly rearranged and renumbered for purposes of analysis later in the present report, one can reproduce the listing as follows:

1. Products produced using one of the following technologies:
    a. DNA/RNA: genomics, pharmacogenomics, gene probes, genetic engineering, DNA/RNA sequencing/synthesis/amplification, gene expression profiling, and use of antisense technology.
    b. Proteins etc. Sequencing/synthesis/engineering of proteins and peptides (including large molecule hormones); improved delivery methods for large molecule drugs; proteomics, protein isolation and purification, signalling, identification of cell receptors.
    c. Cell and tissue culture and engineering: cell/tissue culture, tissue engineering (including tissue scaffolds and biomedical engineering), cellular fusion, vaccine/immune stimulants, embryo manipulation.
    d. Gene and RNA vectors: gene therapy, viral vectors.
    e. Bioinformatics: construction of databases on genomes, protein sequences; modelling complex biological processes, including systems biology.
    f. Nanobiotechnology: applies the tools and processes of nano/microfabrication to build devices for studying biosystems and applications in drug delivery, diagnostics, etc.
2. The use of any of the above technologies in research for health applications.
3. Large molecule recombinant therapeutics, including monoclonal antibodies (MABs), recombinant vaccines, enzymes and hormones.
4. Diagnostic tests (including DNA testing) for genetic conditions and molecular diagnostics for infections, cancer screening, other diseases, and tissue rejection; protein testing using micro-arrays and immunoassays of blood, etc.
5. Molecular imaging (using peptides to bind to receptors) to identify diseases or tumours.
6. Products produced using stem cells, or research into stem cells.
7. Small molecule therapeutics developed through a significant contribution of biotechnology.
    Examples provided include the use of DNA-based molecular methods to identify new active molecules produced by microorganisms, using comparative genomics to identify new drug targets (e.g. comparing metabolic pathways between hosts and parasites), or using other genetic information to identify drug targets.
8. Neutraceuticals (food products with health benefits) produced using biotechnology.
9. Application of pharmacogenomics, based on knowledge of a patient's genetic status, to develop personalised medicine.
10. New methods of producing tissues or organs, including xenotransplantation, tissue engineering to construct *in vitro* organs and tissues, and new tissues produced through stem cells.
11. Bioprospecting to identify novel therapeutic compounds and/or the gene sequences that produce them.

In addition, the report notes the relevance of a number of fields in agriculture, forestry and marine biology where use of biotechnological methods could have effects on the human population, particularly where they influence the production of human food or animal feed, but also where they affect textiles or forestry products with which there is human contact:

12. Agricultural and related products produced using the technologies listed under 1(a) to 1(f) above.
13. The use of these technologies in research for agricultural and related applications.
14. Genetic modification of crops, edible varieties of animals or fish varieties, and insects, using recombinant technology.

15. Development of variants on crops or animals other than by genetic modification (*e.g.* using epigenetics or Marker Assisted Selection (MAS), quantitative trait loci (QTL), genetic maps, high-throughput tools, gene shuffling, etc. These biotechnologies can be used to speed up conventional breeding.
16. Use of DNA fingerprinting and molecular diagnostics for identification (for instance for managing wild stocks of fish or game or for identifying diseases), traceability and food/feed safety applications.
17. Animal breeding technologies such as cloning, in vitro fertilisation (IVF) and technically advanced forms of embryo transfer.
18. Biotechnological improvements to animal husbandry, such as improved nutrition, feed additives, controls on infectious diseases, improvements in disease resistance. This section can include diagnostics and therapeutics, which are also covered under the health scenarios.
19. Use of bio-pesticides, such as GM bacteria that express proteins that block the transmission of viruses by planthoppers, parasites that selectively attack crop pests, etc.
20. Molecular farming of products (spider silk) or chemicals (often pharmaceuticals or diagnostics) expressed in plants or animals.
21. Modification of industrial feedstock crops, such as high-lignin tree varieties for bio-energy, or modified lignin varieties that are better suited for paper or ethanol production.
22. Plant propagation technologies such as organogenesis, cell tissue culture and somatic embryogenesis.
23. Biopharming techniques in which crops or animals are genetically modified to produce pharmaceutical proteins and chemicals.
24. Bioprospecting to identify novel compounds or gene sequences relevant to agricultural, forestry and fishing applications. Examples include new biopesticides or genes that confer nematode resistance.

The mere citation of this listing, with its wide variety of topics, illustrates the need for a reclassification in public health terms if a meaningful public health approach is to be developed. It is true that all these many areas have some biotechnological facet, but beyond this they differ greatly. What is more, the list is obviously growing; some of the areas listed now may not develop significantly in the future, but other areas as yet not conceived are bound to be added to the list as the years pass. How are situations like this dealt with in law?

The question is by no means unprecedented. Most forms of law and regulation, whether civil, administrative or criminal, have to be formulated so as to cover areas in which there is constant change and development. Only when a fundamentally new element appears in society will there have to be new law; most other changes can be dealt with by judicial interpretation of existing law, or occasionally by regulation within the law. Donald Black (1987), in his classic socio-legal study, explains this process very well with respect to the law of economic life;[26] the same happens, however, with respect to the regulation of science, medicine and health care technology. The *scientific process itself* remains in many respects unregulated and free to develop as it will; public health regulation will only be brought to bear on it where some form of risk appears to be emergent, involving for example pollution of the environment, injury to subjects in clinical trials, dissemination of misleading data or the inhumane treatment of experimental animals. Some of the *fruits of the scientific process* may enter society freely on the assumption that they will be employed critically and in a responsible manner. Many, though, will need to be regulated from the public health point of view, either by class or individually, if they bring with them inherent risks (*e.g.* toxicity), if their handling or application demand special precautions or knowledge, or if they are particularly prone to irresponsible commercialisation or use.

[26] Black D. (1976): The Nature of Law. Academic Press, Orland, San Diego etc. at pp. 39 ff.

Before considering how the various matters in the OECD listing are or should be handled in law, it is useful to consider those mechanisms that have developed, particularly over the last half-century, to handle similar public health issues arising as a result of scientific activity. One can then consider to what extent those existing mechanisms do, can or should suffice when dealing with new biotechnological developments.

3. Regulation of the scientific process itself: current structures

The "Biotechnology to 2030" project clearly takes as its starting point the assumptions that research in this field will be carried out by research-orientated bodies – whether in the private or the public sector – and that in the public interest there can be a need to regulate this activity or certain facets thereof. Experience from the regulation of drug research suggests that such regulation is likely to be desirable *firstly* in order to contain possible risks, *e.g.* to trial subjects or to the community or environment as a whole, and *secondly* in order to promote the best use of resources. The latter may involve the development of policies on the use of state resources in this field (*e.g.* for institutional research) and/or the creation of selective incentives for the private sector.

As noted above, society has generally chosen to leave science free to develop in its own way, promoting rather than restricting such development in the expectation that it is likely to serve the common good. Prescriptive law and regulation in the public health interest have only been brought to bear on the scientific process where it has resulted (or appears likely to result) in some form of risk to society. Significant examples relate to human and animal experimentation; the use, control and safe disposal of materials; and the need for transparency.

3.1. Human experimentation

There is a wide consensus that, while this is necessary to medical progress, the risks to the trial subject must not be disproportionate to the goal; the possible risks must have been defined as far as possible in advance and the trial subject must, after adequate explanation, have acquiesced to them. An independent and expert body must have approved the study and must monitor its progress, and there must be criteria for ending the study where this appears advisable. These and other principles have been laid down in general terms by the World Medical Association[27] and in greater detail in national legislation. The manner in which they are formulated renders them applicable to almost any conceivable form of human experimentation, clearly including novel biotechnological techniques or products.

3.2. Animal experimentation

Consensus in this field is less complete but growing. The principles are well illustrated in the relevant Netherlands legislation of 1997.[28] Animal experiments may be conducted only by a qualified licensee; "[a] licence shall permit experiments…only insofar as the experiments are intended to benefit, either directly or indirectly, the health or nutrition of human beings or animals…" Animal experiments shall not be conducted where the required knowledge can be attained in other ways; measures to avoid undue suffering are imposed, and (as in the case of human experimentation) an ethics review committee must give its approval to the experiment. Again, the formulation of this and similar pieces of legislation or regulation is such that they are fully applicable to new fields of study, such as those in biotechnological research. The

[27] World Medical Association (revised 1996): *Declaration of Helsinki on Biomedical Research Involving Human Subjects*. (subject to continuous revision).
[28] *Experimentation on Animals Act*, Netherlands, 1997.

only reservation that one might advance is that, the more novel the area of study, the greater the difficulty of foreseeing and perhaps even recognising risk.

3.3. Use, control and safe disposal of materials

A classic restriction on the use of materials, whether in research or for other purposes, is that relating to narcotics and other controlled substances, where national laws and regulations are almost universally based on global instruments.[29,30] Comparable but different rules apply to the use of radioactive substances. The narcotics rules seek to prevent the wider dissemination of dangerous substances through carelessness or theft; the rules on radioactive substances are concerned primarily with prevention of environmental contamination (*e.g.* through pollution of effluents). There are also rules regarding the disposal of research materials, e.g. destruction of cadavers. Again, it is not difficult to envisage closely parallel rules being applied to certain biotechnological materials, particularly where these might prove dangerous to the community, e.g. by entering the food chain or water supply. To take a slightly more distant analogy: society has for half a century succeeded in keeping the surviving samples of the smallpox virus under strict control in a mere two centres31 and it should surely be capable of ensuring that any dangerous biotechnological vector or form of life is maintained under strict supervision and prevented from escaping into the community.

3.4. Transparency

A relatively new but rapidly developing principle relates to the need for transparency in research and development, *i.e.* the need to avoid the strict confidentiality that commonly surrounds innovation, particularly where it has a pronounced market potential. While on the one hand the scientific desire to publish one's findings and on the other hand the ability to protect intellectual property tend to counter excessive secrecy, there has been mounting concern as regards the concealment of known risks, for example in the course of clinical trials. So long as the emergence of such risks remains known only to the scientists directly involved, the sponsoring corporation and perhaps a single regulatory agency (that is bound to its own confidentiality rules), others may unknowingly be exposed to them. Particularly in the United Kingdom and Canada, but also in the United States, important initiatives have been undertaken both to promote the release of all data from clinical trials[32] and to ensure greater transparency in health research generally.[33]

There is also the related issue of transparency regarding the acts of regulatory agencies; an industrial applicant must clearly be informed as to the reasons for a decision regarding their product, but in some situations the public interest could be such as to require the broader release of data from regulatory files, especially where there are suspicions of risk.[34] It seems very likely that these pressures will have global repercussions in the coming years and such measures are clearly applicable to a much wider range of innovative activities than the drug trials with respect to which they were originally conceived.

[29] Single Convention on Narcotic Drugs (1961). United Nations, New York.
[30] Convention on Psychotropic Substances (1971). United Nations, New York.
[31] CDC, Atlanta, United States and the Vector Institute, Siberia, Russia.
[32] Abbasi K (2004):Compulsory Registration of Clinical Trials. *Brit. Med J.* 329:637-638. For USA see Kimball AB and Weinstock MA: Mandatory registration of clinical trials: A major step forward for evidence-based medicine. J Amer Acad Dermatol, 52 (5) 890-892.
[33] Lexchin J, Mintzes B (2004): Transparency in drug regulation: mirage or oasis? CMAJ, 171, (11). doi:10.1503/cmaj.1041446.
[34] Particularly during the early development of modern drug regulation in the 1960s and 1970s national regulatory agencies were even reluctant, in view of their confidentiality clauses, to share data with one another; this problem has largely been overcome, at least among agencies having similar standards and perceptions of duty.

3.5. Overall impressions

At least in principle, and often in practice, rules have been developed to protect society from unwanted consequences of scientific research activity. In Sections 5, 6 and 7 of this report one must attempt to determine to what extent the above approaches to possible health problems emanating from innovative research are likely to be adequate, given due interpretation, to cover the relatively new field of biotechnology.

Table 1 - Regulation of new drugs for human use: An outline of the principal steps

Regulatory step	***Data required for assessment***
Application for investigational use in human subjects *(regulatory approval is not required in all countries)*	Data on structure, pharmaceutical formulation, purity, short-term stability Animal data on metabolism, pharmacology, acute and short-term toxic effects
Application for marketing licence	Data regarding all animal studies as outlined above; appropriate long-term toxicity studies
	Data on metabolism in man ("human pharmacology")
	1. Basic studies of effects in healthy human subjects ("Phase One")
	2. Limited studies of effects in patients to determine likely therapeutic value and possible adverse effects and indicate possible dosage level ("Phase Two")
	3. Larger-scale studies of therapeutic and unwanted effects and dosage schedules over a longer period (Phase Three)
	Final pharmaceutical data (including longer-term stability studies, packaging form)
	Draft data sheet /package insert presenting claims, dosage, adverse effects, interactions, etc.
Agency: Request for supplementary studies/data	Will be requested to clarify open questions or meet possible concerns
APPROVAL (generally for a period of five years)	May be conditional *(see below)*
Reassessment	After five years; earlier if new claims are advanced or new concerns arise.

Note(s): (1) This is a very much simplified presentation of a process that varies from country to country and may be modified to meet the individual case.
(2) Most countries make provisions for hearings to discuss possible concerns, and for appeals to be lodged against negative or restrictive decisions.
(3) Depending on the nature of the drug, special studies or study designs may be required.
(4) Supplementary studies (e.g. in children, the elderly or particular risk groups, may be required in light of the claims advanced or concerns arising from the animal studies.
(5) Any type of condition may be imposed when approval is granted, especially where this is considered necessary in the interests of safety. In marginal cases, for example, intensive monitoring of all cases may be required for a specified period; in some circumstances one may require follow-up studies of suspected interactions with other drugs.
(6) As noted elsewhere, the drug regulatory process does not generally concern itself with prices or with intellectual property rights, which are the concern of other bodies.
(7) Some national agencies have to grant approval for a new drug to be studied in humans (Phase One above); in other countries this is a matter for ethical review boards or comparable bodies.

4. Regulation of the fruits of research: current structures

4.1. Acceptability of existing health regulation

New products and methods entering the field of public health or health care are regulated by various series of instruments. The principal types of instrument and the scope of each are outlined in the sections that follow. Much of the debate on the merits and possible dangers of this form of regulation revolves around the field of human drug regulation, some typical characteristics of which are summarised in Table 1 above.

Before embarking on this review one must deal with a type of criticism of existing health regulation that is sometimes voiced, one that is noted in the current OECD scenario: arguments to the effect that it can inhibit innovation and seriously delay its implementation in the field, and that during the latter half of the 20th century it indeed did so.[35] This belief has been propagated in various fields, but most markedly as regards the regulation of new drugs. It is relevant to the present discussion, since from various sides the view has been advanced that even well-intended regulation could pose a threat to innovation in the field of health biotechnology. An argument particularly favoured by prominent critics of regulation is that extensive pre-marketing assessment of a product should in part be replaced by in-field monitoring of efficacy and safety in the field after marketing ("living licences"). In the present view this approach, reflecting very much the views on "deregulation" propagated by the late Dr Lou Lasagna some forty years ago, is dangerous. Several points are relevant:

1. The major drug regulatory systems arose in direct response to drug calamities (such as those associated with the names of Salvarsan, Elixir of Sulfonilamide, Stalinon and Thalidomide).[36] The fact that some serious disasters continued to occur led to a progressive strengthening and wider adoption of regulation, a process that generally continued until the 1970s.

2. After 1970, an industrial dislike of regulation, and particularly claims that innovation was being inhibited,[37] secured some political support. It is beyond reasonable doubt that in some situations, and particularly in the United States, regulation had become excessively bureaucratic and had overreached itself; introduction of new drugs was at that time delayed considerably longer than in Europe. Particularly in the United States, approval by the FDA was – as a result of this debate and following considerable corporate pressure – accelerated[38] and simplified.

3. No comparable relaxation occurred in Europe, though a greater degree of consultation with industry was introduced in all countries. Technical assessment appeared to justify the need for maintaining firm pre-marketing standards. In most countries, assessment of new drug applications was completed within a 90- to 120-day period

[35] OECD Health Scenarios, Third Report (Draft) 2007 at page 4.

[36] See review of drug disasters by Dukes MNG, Mildred M and Swartz B (1998): *Responsibility for Drug-Induced Injury* (Second Edition); IOS Press, Amsterdam and Tokyo, at pp. 3-16.

[37] This process was largely managed in and from the United States by the industry-funded Center for the Study of Drug Development, sited initially at the University of Rochester and subsequently at Tufts University, Boston MA. The Center both undertook studies of its own and sponsored papers by a range of academic workers who were supportive of its views. The Center did demonstrate a progressive fall in *new drug introductions* but this reflected almost exclusively the abandonment of efforts to market "me-too" variants on existing products, not a fall in medically valuable innovation (see Figure 2). It is striking that the principal decline in the introduction of new or novel drugs actually followed the relaxation of US rules in 1984-94 rather than preceding it.

[38] Up to about 1980, the drug approval process at the US FDA was markedly slower than in Europe. In countries such as the Netherlands, applications had to be dealt with within 120 days of submission, and the deadline was only very rarely missed.

prescribed by law. Comparisons of regulatory work in several countries also indicated, however, that approximately one-third of new drug applications had to be rejected for scientific reasons relating directly to the public interest.[39]

4. Any attempt to release medicines for marketing without full assessment must be based on a considerable degree of trust in the competence and honesty of the manufacturer. During the last thirty years a series of disasters attributable directly to the suppression or distortion of data by both major and minor firms has unhappily undermined much of that trust.[40] Notable was the massive tragedy of Vioxx, attributable to the suppression by Merck Inc. of data on the drug's cardiotoxicity; in the case of triazolam, Upjohn had withheld from the regulators all reports on the psychotoxicity of the doses proposed for marketing; directly relevant to the matter of "living licences" is the case of benoxaprofen (Lilly) where the UK authorities permitted marketing on the basis of a "gentlemen's agreement" to continue clinical studies, despite rejection of the drug in Benelux for lack of proof of safety – the result being the death of more than 200 elderly Britons.[41] Sometimes, too, data are forged; the drug calcium dobesilate, for example, was claimed to "cure" diabetic retinopathy on the basis of a file in which successive retinograms showing decline in a progressive case were presented in reverse order.[42]

5. It is true that systems have been created to gather data from the field on adverse effects of drugs subsequent to marketing, but these are relatively slow and very incomplete; only a small minority of physicians participate. These systems often suffice to gather early information on entirely unanticipated effects, but the information obtained is not quantified since the reporting rate is not known, and is generally so low.[43] Nor is it generally possible in the field to obtain a confirmation of supposed efficacy if this has not been established at the time of marketing.

6. Where relaxation of rules results primarily from corporate pressure on the political establishment, this can disastrously override technical considerations – as exemplified by the events in 1994, when in the United States a wide range of products were removed from FDA control.[44, 45]

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[39] See studies cited by Dukes G (1985): *The Effects of Drug Regulation.* MTP Press, Lancaster and WHO Regional Office for Europe.

[40] The examples given in the main text are public knowledge. When, as is the experience of the present writer, one has as an expert witness access in court cases to unpublished material, one is even more strongly inclined to dismiss the image of "Big Pharma" as an ethically minded and responsible element in society. Gross misrepresentation of data is unhappily common. In recent civil proceedings between two companies, where the plaintiff brought accusations of improper behaviour against the defendant, it was not difficult to advance evidence of the plaintiff company itself having been found criminally guilty of multiple offences in a single country in the course of a single year. These were not mere administrative misdemeanours, but matters in which the firm had acted directly and knowingly in a manner endangering the public interest.

[41] These and other cases are reviewed by Dukes MNG. (2005): The Law and Ethics of the Pharmaceutical Industry. Elsevier, Amsterdam etc.

[42] Personal records.

[43] A classic study of this problem was that in the United Kingdom by Walker SR and Lumley CE (1986) Reporting and Under- reporting. In: Mann RD (Ed.): *Adverse Drug Reactions.* Parthenon Publishing, Carnforth and Park Ridge NJ. They found that, even in a study where physicians were fully aware that their reporting of supposed adverse effects was being examined, only some 15% of severe or moderately severe adverse effects were notified to the reporting system. The situation has not changed greatly since 1986, and in many countries the reporting rate is far lower; an FDA official expressed the view to the present writer in 1992 that in the United States much less than 1% of those reactions that should have been reported were in fact notified.

[44] US Dietary Supplement Health and Education Act 1994.

[45] A large number of cases of cardiac complications, including fatalities, followed the deregulation of *Ephedra*-based products under the 1994 Act.

7. The mistaken view that the effects of regulation are purely negative and obstructive overlooks not only its role in protecting the public, but also its positive contribution to research and development. Anyone who has participated over a long period in contacts between innovators and regulatory authorities will be aware of the extent to which scientific regulators assist firms in understanding the manner in which particular types of work can best be designed and conducted.

8. Above all, the fantasy that regulation has, by and large, unnecessarily impeded research and development is without any serious foundation. It is based largely on anecdotal data and selective analysis. It is instructive in this connection to view the data in Figure 2, based largely on evidence gathered by the industry-based Tufts Center itself. Over a long period prior to the growth of regulation, new drugs were marketed in increasing numbers. What ultimately did go into – perhaps terminal – decline towards the end of the 20th century was the massive introduction of non-innovative products of dubious merit and value. The steady flow of truly innovative items – much fewer in number but contributing immensely to the progress of medicine – continued unabated. If the growth of regulation did indeed have any major effect on the development process then it was the entirely laudable one of reducing the flow of unnecessary "me-too" products contributing nothing to the advance of medicine.

9. Suggestions that requirements regarding clinical trials should be simplified by employing more advanced techniques or more subtle measures or biomarkers tend to overlook the fact that efforts to this end are being made all the time. Clinical pharmacologists, who are influential participants in the regulatory process, undertake much research work in this direction; industry itself is constantly seeking and developing better and less burdensome methods of obtaining evidence of efficacy and safety; and regulatory authorities themselves do much to improve the efficiency of the clinical investigational process.[46] Similarly, suggestions that recruitment of patients for clinical trials should take account of their genetic data and material accessible through their patient records are in essence correct – this enables one to compose homogenous patient groups and subgroups - but where possible these approaches are used already. Finally, it has been suggested that some agencies demand unnecessarily large clinical trials – the figure of 20 000 has been mentioned. The source of this figure is not clear, unless it relates to post-marketing follow-up ("Phase Four studies"). Neither agencies nor sponsors have in fact an interest in unnecessarily large trials, which represent a waste of effort and expense; the optimal size of a trial depends on the drug and its proposed use, and is often the subject of fruitful advance discussion between the agency and the sponsoring firm.

Directly relevant here is the fact that drug regulation (like various other forms of public health regulation) has always been distinguished by its flexibility. *Whatever caricatures may have been drawn of them, most regulators are not faceless bureaucrats; they are physicians, pharmacists and other scientists, commonly with research experience and entirely capable of interpreting the rules to suit the individual case, always with the public health interest taking centre stage. The real decision-making power in most agencies lies not with full-time civil servants but with committees of experts normally engaged in scientific or medical work.* A promising drug and an honest applicant meriting lenient treatment will get it. It would be very risky to attempt to modify the law and regulation so as to impose lesser (yet still standardised) demands on any class of products as if they all merited the same approach. This flexibility is perhaps the strongest point in existing drug law and regulatory practice.

[46] An excellent example is the US FDA's "Critical Path Initiative" developed since 2004 to further the progress of regulatory and developmental science. See Dr Jane Woodcock's "Commentary on the CP initiative", 17 August 2007. http://www.fda.gov/oc/initiatives/critical path/commentary.html.

As of 2007 it seems very unlikely that any call to relax official involvement with the drug sector much further or faster – for example, with a general shift of Phase III studies into the post-marketing phase – will be regarded as seriously credible. No-one would argue that health regulation in the drug field is perfect – mistakes do get made – but its record suggests that it is a great deal better than any alternative that has yet been devised, that it forms a good model for dealing with the fruits of biotechnical innovation, that it is getting progressively better, and that one would be well-advised to avoid tinkering with it.

No apology is therefore needed for placing a heavy emphasis in this section of the report on the established traditions in the regulation of drugs for human use. Although, as we have seen in Sections 1 and 2 of this report, biotechnology is likely to impact increasingly on health at many points, one of its most important fruits will probably continue to be the development of novel therapeutic agents for use in man. In 1996 a report by Lawrence noted that in Europe no fewer than 37 of the existing 122 biotechnology firms were engaged in projects having a therapeutic purpose and 12 in diagnostics; of 329 biotechnology firms in the United States, 49 were engaged in therapeutics and 22 in diagnostics.[47] A year later, in 1997, a report on the US situation similarly found that of firms engaged in biotechnology, some 29% were primarily interested in therapeutics and a further 17% in diagnostics,[48] and the pattern does not seem to have changed since that time. The consequences of this concentration of effort were already evident at that time in terms of the numbers of new products of biotechnological origin receiving the approval of drug regulatory agencies, and it is notable how many of those products represented notable advances at a time when research of the more traditional type was producing relatively little of real interest. The same 1997 report, bearing the authoritative imprint of the US Office of Technology Policy (of the Department or Commerce), listed as particularly prominent human therapeutic fruits of biotechnological research up to that moment: recombinant insulin and human growth hormone, Alpha interferon, OKT3 (a monoclonal antibody used to treat kidney transplant rejection), a number of vaccines, blood clotting factor VIII (MAB purified or of rDNA origin), tissue plasminogen activator, erythropoietin, gamma interferon, gluco-cerebrosidase, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, interleukin-2, beta interferon, dornase alfa inhalation solution, ReoPro (a monoclonal antibody used to reduce clots in angioplasty procedures), Avonex (recombinant beta interferon 1a used for relapsing multiple sclerosis) and various forms of human growth hormone. All of these products had by 1997 passed the regulatory phase unscathed, all had proved therapeutically valuable, and none has then or since proved disproportionately risky in use,[49] suggesting a successful balance between innovation and safety regulation.

Again, the picture does not seem to have changed a decade later. Although without access to current internal data one does not know what proportion of *applications* for innovative new drugs reaching regulatory bodies today concerns products of biotechnological origin, it is striking to see how, since 2000, the number of *approvals* granted to new biotechnological products originating with small firms has overtaken the number of drug approvals granted to

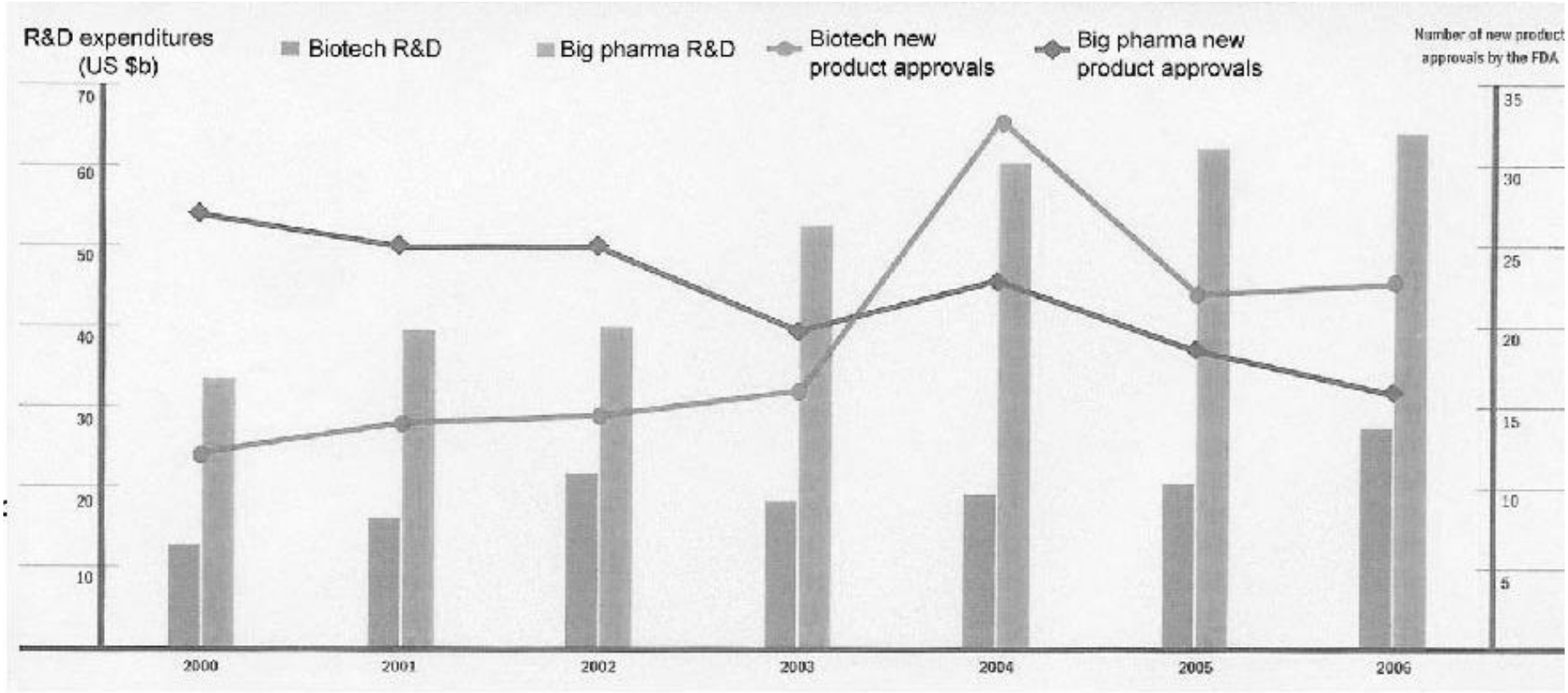
[47] Lawrence S. (2006): State of Biotech Sector – 2005. *Nature Biotechnology*, 24(6): 603.
[48] Paugh J, Lafrance JC (Eds) (1997): *Meeting the Challenge: US Industry Faces the 21st Century. The US Biotechnology Industry.* US Department of Commerce, Office of Technology Policy, July 1997, at page 28.
[49] Based on consultation of Aronsen J.K. (Ed.) (2005) *Meyler's Side Effects of Drugs*, 15th edition. Elsevier, Amsterdam, New York etc. and the corresponding *Side Effects of Drugs Annuals.* Naturally, as experience is gained with these new products, views on their efficacy/safety ratio may change, and their field of use may as a result expand or contract. The erythropoiesis stimulating agents (ESAs) provide an example. When they were found to produce antibody-mediated pure red cell aplasia in a minority of cases, vigorous controversy arose as to their continued use for treating the anaemia of renal failure [see Locatelli F *et al.*, *Nephrol Dial Transplant* (2004) 19: 288-293, who did not consider them "disproportionately risky" in this serious indication.) On the other hand, the acceleration of tumour growth in a proportion of patients with cancer receiving ESAs to treat anaemia has very recently led the FDA to define their use for this purpose more narrowly.(See: www.fda.gov/medwatch/report.htm ; issued 3 January 2008).

the “Big Pharma” companies (Figure 1).50 This figure also illustrates the fact that during the last decade drug regulators must have accumulated a great deal of experience in applying law and regulation to the field of biotechnology-based products.

Such considerations are, however, of only limited relevance to truly innovative biotechnological products of the type under consideration in this report, since these are likely to differ so much from traditional synthetic drugs. In some respects they are probably much less risky (cell toxicity), yet in other respects they may be much more so (unforeseeable induction of biological imbalance). If one is obliged to speculate, one would venture to anticipate that with respect to biotechnological products the regulatory regime will be adapted rather than weakened; for individual products it could well be tightened in some respects and relaxed in others (see Sections 6 and 7 of this report).

[50] Figures 1 and 2 in the present report can usefully be set alongside Figures 1 to 4 in the OECD report “Human Health Biotechnologies to 2015”, Paris, May 2007.

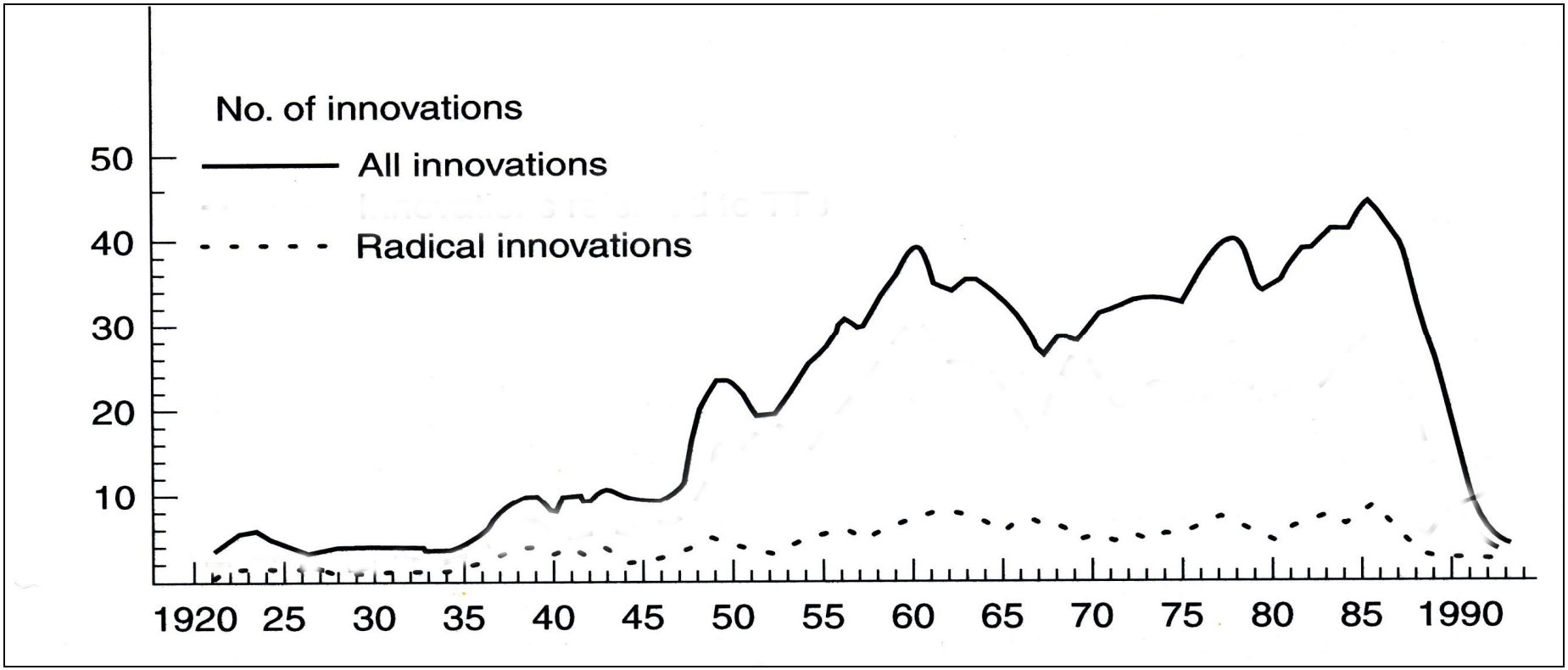
Figure 1 - Spectrum of approval for innovative drug products, 2000-06[31]



The vertical columns represent annual expenditure on R&D 2000-2006; the shorter (dark grey) columns relate to the biotech industry and the longer (light grey) columns to "Big Pharma". The figure shows the number of new product approvals yearly, with the Biotech industry overtaking the Big Pharma companies in this respect after 2003, despite a much lower R&D investment. FDA approvals are shown in the last column.

[31] Figure contributed by Dr Koen Wiedhaup, based on international data from the FIGON Innovation Committee, 2007. FIGON is the Federation for Innovative Drug Research in the Netherlands.

Figure 2 - The irregular course of drug innovation: 1920-1970[32]



The relatively small proportion of new drugs that are therapeutically innovative is striking.

[32] Edited for the present purpose from a figure published by Achillidelis B and Antonakis N (2001): The Dynamics of Technological Innovation: The Case of the Pharmaceutical Industry. Res. Policy, 30, 535-538.

4.2. The essence of human drug law and regulation

In the health field, the most likely type of output of biotechnological research is in the form of a marketable product. As already intimated, the question of regulating market approval of products for human use based on biotechnological innovation can benefit from experience gained over a long period in the regulation of new drugs. While such regulation can in some form be traced back for a several centuries, modern forms of drug regulation have evolved over several decades (Norway 1928, Sweden 1935, U.S.A. 1938); there was considerable acceleration of the process from 1960 onwards and a degree of international harmonisation thereafter. Concerns in society, leading to regulatory measures, related at first largely to issues of *quality*. In due course broader policy approaches were adopted, bearing in turn on matters of *safety, efficacy* and *truth* (*i.e.* the provision of reliable and adequate information). Each of these components was added to drug regulation because, as noted above, worldwide experience (sometimes tragic) demonstrated the need for it. These four policy elements remain basic to drug regulation. A more general issue, noted already in Section 3.4. above, relates to the need for *transparency* with respect to the acts of all parties, including the regulatory agencies themselves. Matters of *intellectual property* may be tackled by drug regulatory bodies or other agencies; they will largely be left out of consideration in the present analysis, since they concern an economic issue rather than one of public health.

Experience in the field of drugs underlines the fact that regulatory standards in the health field are unlikely to be absolute: no drug is 100% safe, 100% effective or even 100% pure. In practice society demands in these respects that the product be *sufficiently* safe, effective or pure to serve its purpose – *i.e.* a "common sense" standard is applied.[33]

The precedent provided by human drug regulation is at all events one of the most important when seeking to identify an adequate starting point for the regulation of new biotechnological products. The definition of a new drug provided in various national laws from the 1960s onwards was very broad indeed and clearly designed to take account of future developments: "A medicine or drug is…a substance or complex of substances which is administered to man or to animals in order to prevent, diagnose, alleviate or cure a disease, to relieve a symptom, or to modify bodily function in some way."[34]

The mention of animals actually extended the scope of regulation into the veterinary field, though the latter has generally been dealt with under separate though parallel laws (see below). The term "diagnosis" extended it to diagnostic agents provided these were actually administered to the patient; the phrase "to modify bodily function" was originally devised to cover the oral contraceptives, but can also be interpreted to cover other non-therapeutic agents such as tonics, sexual stimulants or drugs to address erectile dysfunction.

The most striking use of this broad definition, as drug regulation developed, was to incorporate the hitherto largely separate regulation of vaccines, though for organisational reasons vaccines are in various countries still regulated separately.[35]

In some legislation, the definition is broadened further to encompass all those products for which medical uses are "claimed", irrespective of whether the use is accepted; this enables the

[33] The Netherlands Medicines Act of 1958 classically referred in these matters to the standards that would be applied by a reasonable, thinking individual.

[34] Definition cited by Dukes (2005) The Law and Ethics of the Pharmaceutical Industry. Elsevier, Amsterdam, Boston at p. 3. There are numerous variants on this definition, some extending it in various directions.

[35] The usual reason is that vaccine legislation often predated drug regulation, providing in some countries for manufacturing by a state institution (*e.g.* in France and Denmark); rather curiously, such institutions were then charged with handling vaccine regulation and thus in effect with their own supervision. In recent times, vaccines have largely been regulated in the same manner as drugs though the criteria for risk acceptance and approval can differ, a vaccine normally being administered to a healthy individual. See Section 6.1. of the present report.

machinery of justice to be applied to products such as "medical cosmetics" (claimed for example to relieve acne) or foods claimed to improve health.

Criticism of regulation on specific technical points has often related to the extensive requirements frequently set for the performance of chronic toxicity studies in animals or long-term ("Phase III") therapeutic studies in man, as well as the introduction of strict and obligatory standards for "Good Manufacturing Practice" (GMP) for these products. Each of these merits specific consideration when seeking to apply current drug regulatory standards to products of a novel type emerging from biotechnological research.

a. *Chronic toxicity studies in animals* – These requirements were originally devised to deal with new chemical drugs that acted essentially by exerting toxic or inhibitory effects on particular systems. At times the demands were clearly excessive and they were sometimes modified by consensus;[36] the extent to which they are applicable to an individual product of biotechnological origin will vary greatly with the nature and proposed use of the product.

b. *Phase III clinical trials* – Long-term human studies are primarily justified for drugs that will be taken over many years, *e.g.* to relieve chronic and incurable conditions. Particularly where a drug has certain toxic effects these may not become manifest in short-term work. However, there are well-documented cases in which failure to impose a sufficient requirement regarding long-term work when the need for it had been suggested by animal or other findings resulted in widespread human suffering and death.[37]

c. Again the relevance of the usual demands to biotechnological products will depend on their nature and uses rather than the fact that they originated in biotechnology.

d. *Good manufacturing practice* – It is possible to define extraordinarily high manufacturing standards for drugs, but they are costly and not necessary for all types of product. Here it seems very likely that the manufacturing standards for some products of biotechnological origin will be unusually strict, *e.g.* because of the fact that they may be unusually potent or subject to contamination with highly potent viruses or other materials.

In summary, it seems very likely that, when applying drug regulation to entirely novel products of biotechnological research, it is precisely the established tradition of intelligent flexibility that will prove vital. Some of these products will by their nature be expected to produce only a brief and transient effect, perhaps tonic or stimulant, and their acceptability will be demonstrable in short-term work, though sometimes with a need for long-term follow-up. Others may by their very nature (*e.g.* effects on genetic material) appear capable of exerting very late and even multigenerational effects, and in such cases the requirements that society must set for their acceptance may actually exceed considerably those normally imposed on more familiar forms of treatment with chemical drugs.

[36] In Australia there was for a time a requirement that certain studies involving dogs and monkeys be conducted for seven or ten years; ultimately it became clear that animals of these ages might be subject to senile degeneration, and it was also shown that all the late findings emanating from such studies could in fact be detected in investigations lasting less than a year.

[37] It seems likely that the case of benoxaprofen in Britain is relevant; this drug, which proved highly hepatotoxic in certain elderly users, had been refused in a number of other countries; the compound had some unusual pharmacological properties that seemed to indicate a need for specific evidence of long-term safety in human subjects. See also Section 4.1. above.

4.3. Veterinary drug law and regulation

Laws and regulations on veterinary drugs and vaccines are in some respects very similar to those covering products for human use, with the emphasis on quality, safety, efficacy and the provision of appropriate information. Important *additional provisions*, however, relate to those situations in which animals provide sources of human nutrition (meat from slaughtered animals, eggs, milk). Where drugs and vaccines are concerned, these provisions concern primarily the need to ensure absence of active drug residues (*e.g.* growth hormones in meat, antibiotics in milk). When interpreting or extending this legislation to deal with new biotechnological products the same will apply, but it is conceivable that certain of these products will bring about changes in the nature and composition of the edible animal product that could have repercussions for human consumers. Possibilities are legion, but effects might for example take the form of changes in the antigenic properties of milk (relevant for milk allergies) or in the quantitative composition of meat (*e.g.* variation in content of fats or water). Perhaps to a greater extent than where drugs for human use are concerned, the requirements set by regulation will need to be adapted to the nature and properties of the individual product.

4.4. Phytopharmaceuticals and pesticides

This heterogeneous group of regulations may be considered as a whole; they have developed in the recent past primarily to cover chemical substances used in agriculture to influence the health or growth of plants or to reduce infestation with pests of various types. As in the case of veterinary drugs, the public health concern has related largely to the risk of residues in edible material, but in this case also to environmental contamination and derangement of the environmental balance (*e.g.* as a result of the elimination or modification of natural predators). In both respects one is likely to encounter existing rules which, with only a little extension and interpretation, are likely to prove applicable to those products of biotechnology that serve the same purposes as existing phytopharmaceuticals and pesticides. The exceptions will apply where a biotechnological product proves capable of eliminating an unwanted species entirely, or changing its nature, thereby disturbing the biological balance.

4.5. Laws on foods and nutrients

So long as foodstuffs were largely produced and handled in a traditional manner, no specific public health laws dealt with them, though civil and statutory rules did emerge relating to their proper handling. Mass production and the use of entirely new substances in foodstuffs (*e.g.* dyes, artificial sweeteners) changed this situation, rendering it necessary to set standards for individual types of food and in certain cases for the use of particular substances in foods for human consumption. In the European Union, for example, the extensive listing of "E-numbered substances" creates firm rules with respect to these materials (*e.g.* flavourings, colorants). Simultaneously, there has been widespread adoption of rules for food labelling, backed by systems of inspection; specific rules govern the mode and degree of use of these substances and the claims that may be advanced with respect to them.

Generally speaking, this complex and evolving legislation seems likely to be well suited to dealing with the inclusion in foods of new substances emerging from biotechnological research. It would also seem applicable to the modification of existing basic components of the diet (proteins, fats or carbohydrates); US food law has for example been applied to require approval of modified fats that resist alimentary absorption ("Olestra") and a sweetener

("sucralose") that is claimed to be derived from sucrose but that is not metabolized;[38] both products are intended to assist in slimming diets.[39]

4.6. Environmental law and regulation

A few forms of environmental law and regulation are old. Originally in the realm of civil law (notably that of "nuisance", with pollution of the local environment comprising a ground for civil action and compensation), they developed through the concept of "criminal nuisance" into legal standards and specifically defined offences in the law applied by local or national authorities (*e.g.* in sanitary law and factory regulations). In recent decades, much more widely defined standards have emerged, *e.g.* with respect to water and air, though they are still in a phase of evolution. As in other fields the public health concern has generally been with dissemination of toxic substances, but also with the spread of infection. As the law in this field currently exists, there would seem to be no great difficulty in applying it by interpretation or modest extension to products emerging from biotechnology if these enter into the environment more than incidentally and particularly when they are non-degradable or even (in the case of microorganisms) self-replicating.

4.7. Law and regulation concerning interference with genetic processes

Concern with health risks that could emerge from interference with genetic processes has developed much more recently than the other public health concerns outlined above, and the law is still immature. Controversy has emerged regarding not only interference with the human genome but also as regards genetic modification of animal and plant species having a close association with human welfare, especially those used as a source of food. Discussion has related both to intentional modification of genetic processes and to incidental or accidental changes of this type in the course of biotechnological innovation.

4.8. Regulation of prices

Drug prices are not as a rule regulated by drug approval bodies, which deal only with scientific issues. In developed countries, prices of drugs are generally a matter for negotiation between the manufacturer and the agencies handling the financing and purchasing of drugs for the public sector, while drugs sold in the private sector are free of control. Health insurance agencies and health services do therefore exercise an important measure of control on prices, and where no agreement can be reached a drug will be ineligible for use in the public sector. Highly innovative drugs, a group which already includes many products of biotechnology, will be expected by their originators to benefit from high prices and generous profits, and considerable difficulties have already been encountered on this score. It is not unlikely that, where an innovation is such as to merit widespread use, there will be increasing government intervention in an attempt to set prices that are affordable for the public budget but still provide a reasonable reward for the originator.

One suggestion that has been advanced is that regulatory approval of drugs for marketing might be accelerated by ensuring that such approval should incorporate a guarantee that the product will also be eligible for payment or reimbursement by the appropriate bodies. This is

[38] Michael A. Friedman, Lead Deputy Commissioner for the FDA, Food Additives Permitted for Direct Addition to Food for Human Consumption; Sucralose Federal Register: 21 CFR Part 172, Docket No. 87F-0086, 3 April, 1998.

[39] It should be noted however that neither product has been widely approved outside the United States and that the use of both Olestra and sucralose has been criticised on safety grounds. See Internet papers discouraging the use of Olestra on safety grounds, issued by the Centre for Science in the Public Interest (www.cspinet.org/olestra). For criticism of sucralose see "The Truth About Splenda" website sponsored by the Sugar Association (www.truthaboutsplenda.com/); the latter disputes the promotional claim that sucralose, a chlorine-containing compound, is derived from sucrose.

not realistic. Drug approval bodies are constituted in such a way as to ensure competent assessment of efficacy, safety, quality and presentation. Prices and eligibility for reimbursement require separate assessment by a differently constituted body with economic insight into costs and capable of balancing costs against the relative merits of the product as already assessed at the regulatory level.[40] One may note that some decades ago the regulatory system in France did provide for simultaneous assessment of efficacy, safety, quality and pricing, but the arrangement appears to have slowed regulatory approval rather than accelerating it, and it was abandoned.

4.9. Regulation and intellectual property rights

Although issues of intellectual property and biotechnology are being dealt with in a separate OECD report, we must draw attention here to an ongoing and very vexed question, relating to the possible role of health regulation in ensuring protection of intellectual property. This is likely to be of great importance where products of biotechnology are concerned.

From the outset, as noted earlier, the regulation of drugs and vaccines has been concerned with issues of health; the product must be reasonably safe, effective and of good quality, and the information provided on it must be reliable. Also from the outset, however, drug manufacturers have been concerned by the possibility that information might in one way or another "leak" via the regulatory agency from one firm to another. For that reason, clauses regarding the confidentiality of material in regulatory files have long been part of the law.

As patents began to expire on many original drugs, opening the road to generic copies, the owners or original products increasingly sought to interpret these confidentiality clauses in such a manner that agencies would not be allowed to use their prior knowledge of the properties, efficacy and safety of the primary product in assessing an application from a later generic competitor (the so-called doctrine of "data exclusivity"). That means that the generic firm would be obliged to repeat all the pharmaceutical, toxicological, clinical and other studies in order to secure registration. This would form a serious barrier to generic supply. Both experts and consumer advocates have strongly opposed this interpretation, pointing out that repetition of this work would be wasteful and unethical, but also that by the time patents expire and generic products are offered the essential facts regarding the efficacy and safety of a drug have become generally known and acknowledged, with much of the necessary information available to all in the medical literature. Regulation, it is argued, is concerned with health issues and not with intellectual property rights.

All the same, recent drug legislation has tried to make some allowance for the fact that patent protection alone may be insufficient to protect an innovator who has invested heavily over a long period in development work in order to secure registration of his product, and needs time to secure an adequate return from the market on this investment. Revised rules promulgated by the European Union in 2004 reflect this view.[41]

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[40] See account of the Australian Pharmaceutical Benefits Scheme in Dukes MNG (2005): The Law and Ethics of the Pharmaceutical Industry. Elsevier, Amsterdam, Boston etc. at page 228. A broader account of price approval mechanisms is provided by Dukes MNG, Haaijer-Ruskamp FM, de Joncheere CP and Rietveld AH (Eds) (2003): Drugs and Money (8th Edition). IOS Press, Amsterdam, for WHO/Europe, Copenhagen.

[41] The issue is too complex to be fully reflected here. Essentially, the European rules of 2004 introduce a harmonised EU eight-year data exclusivity provision with an additional two-year market exclusivity provision. This effective ten-year market exclusivity can be extended by an additional one year maximum if, during the first eight of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. This so-called 8+2+1 formula applies to new chemical entities (NCEs) in all procedures and to all member states (unless certain new member states are awarded derogations, which they can request following publication of the new law). In practical terms, this means that a generic application for marketing authorisation can be submitted after Year 8, but that the product cannot be marketed until after Year 10 – or 11. It may be noted that data exclusivity is granted for five years in the United States and Australia.

Where synthetic drugs are concerned, this is a relatively black-and-white issue; either a generic drug is chemically identical to the original product, or it is not. In the latter case it is a new drug and a full investigational file will be required. If the differences from the originator product are slight, and relate only to the pharmaceutical formulation, some supplementary work on tolerance or bioavailability may be required, but that is all.

Where biological products of various types are concerned, the issues are more complex. One does not have the all-or-none issue of chemical identity as a starting point. If known, it may not even be relevant. Two versions of a biological product, produced in similar but not identical ways or from different starting materials, may differ in composition yet be identical as regards their efficacy, safety and usefulness in medicine, and relatively little work may be needed to show that they are mutually replaceable. What that work will need to comprise will have to be determined from case to case, but the basic principle underlying health and drug regulation will continue to apply: one will have to be reasonably satisfied that in terms of efficacy, safety and quality, the "biogeneric" is a perfectly acceptable alternative to the original. Whether it breaches the originator's rights as an innovator will be a matter for the patent authorities to decide.

A footnote: while the above reflects current and anticipated developments in the light of the situation to date, it is not impossible that within the period between now and 2030 society's views on the data exclusivity issue will change again. The present provisions in areas such as the European Union, Australia and the United States have come into being to accommodate the interests of the "Big Pharma" companies as they now exist. With the continuing growth of the generic industry and of consumer advocacy and the new dynamics of drug development resulting from biotechnology it seems very likely that recent regulatory provisions on data exclusivity will need to be revised in the coming years.

4.10. Other relevant fields of law and regulation

The above overview of the existing types of health regulation that might be relevant to biotechnological advances is obviously not exhaustive, but it indicates the considerable potential of existing regulation to deal with many anticipated (and as yet unanticipated) problems by relatively simple adjustment or interpretation. Several other fields are insufficiently relevant to this topic to merit extensive discussion here. *Substances and products intended to be placed permanently in the body* have been dealt with in various countries in regulations on surgical materials or (where they are intended to release a medicament, as in the case of some subdermal implants) under drug law. The plastic-based bone substitute ostamer, intended for use in orthopaedics, was considered to fall under US drug law but proved too dangerous for use and was not, so far as is known, the subject of a full evaluation by the Agency.

In addition to these specific fields, most or all countries have legal regimens to deal with *wares* as a group, and these are applied (supplemented by specific regulations or ministerial orders where necessary) to deal with products not covered elsewhere, ranging from cosmetics to bioactive household detergents.

Regulators have sometimes found themselves faced with submissions for approval of products that they would not normally regard as falling within the scope of their work; there is something of a risk here that the law may, in order to ensure its comprehensive application, be stretched to the point where a purely commercial innovation secures a licence and thereby gains an aura of scientific approval. This has sometimes been the case with the term "nutraceutical", devised in 1989 in Italy by the scientific adviser of a manufacturing company

in order to promote the widespread use of the amino acid carnitine[42]; to my knowledge this fictitious group of products has never gained any scientific recognition, though the term continues to be used inconsistently in pretentious marketing, e.g. of ordinary foods, of special foods "enriched" by the unnecessary addition of vitamins or minerals, and even of herbal remedies and vitamins.43 (See also Section 6.6). It is not entirely unthinkable that biotechnological innovation might in the future produce an entirely new and superior nutrient, but nutritionists confirm that this is not the case up to the present.

4.11. Overview

The above overview strongly suggests that the existing complex of laws and regulations is sufficiently flexible to handle most, though not necessarily all, of the new situations arising as novel products and substances having the potential to affect health emerge from biotechnology. Technical regulation of this type is not in force in every part of the world, but its presence in the major markets, as well as its approval in general terms by international bodies such as the World Health Organization and the Food and Agricultural Organization, means that any significant innovation is likely to be required to meet appropriate standards. In theory, a novel product or technique might be introduced in a minor market where there are no existing regulatory barriers, but the financial burden involved in development, manufacturing and marketing is such that no innovator or firm is likely to seek to exploit a novelty in this way; any attempt to do so would in any case, given the intensive global interchange of information, immediately elicit a major reaction.

In the first instance, a new product, of a type not envisaged when the relevant laws and regulations were drafted, is likely to be dealt with by intelligent interpretation of the original rules having regard to their role in serving public health. When a new class of products is clearly emerging and seems to call for appropriate regulation, that regulation can be drafted. Implementation of such adapted rules should preferably be entrusted to existing and experienced regulatory bodies, or to specialised sub-units of these bodies[44], so as to ensure consistency of action across the board.

The following sections of this report will examine this hypothesis in the light of relevant laws and regulations in a number of markets.

5. Applicability of current regulatory systems to biotechnological innovation: A selective overview

The overview of existing legislation and regulation that follows is selective, and intended to illustrate some current trends in major countries and communities. Because of the rapid development of policies and rules, reference will generally be made only to instruments entering into force during or since 2001.

5.1. The United States

While the United States possesses all the specialised agencies of the types reviewed in earlier sections of this report, it has also led the way in providing co-ordination of the work of these agencies where the need arises, to ensure that new biotechnology products are safe for the environment and human and animal health. The so-called *Co-ordinated Framework for*

[42] Carnitine is normally synthesised in the body and there is generally no reason to provide it as a supplement. The present writer was in the audience at the meeting on Lake Como where the term was launched, by Dr Stephen Deeflice, specifically as a commercial tool to promote sales.
[43] Advice provided by Dr E. Helsing, Nutrition Physiologist.
[44] There are precedents for this: subcommittes of (human) drug regulatory agencies are frequently created to deal with vaccines, veterinary products, homeopathic medicines or other specialised preparations demanding special experience.

Regulation of Biotechnology dates in its essentials from 1986, since when the laws and policies in the various specific fields have been adapted to deal with this area. Agencies concerned are the US Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS), the US Environmental Protection Agency (EPA), and the Department of Health and Human Services' Food and Drug Administration (FDA). Depending on its characteristics, a product may be subject to review by one or more of these agencies.

- *Human experimentation* – The widespread publicity accorded in the United States to revelations of inadmissible experiments in humans led to early passage of regulations, primarily with respect to clinical trials of medicines, designed to prevent abuses. The current regulations in force, which are implemented by the FDA, are designed principally to ensure the completion of adequate pre-clinical studies, the competence of the investigator, the provision of full and understandable information to the trial subject, involvement of an institutional review board, use of an adequate trial design and publication of the results. While designed primarily with new drugs in mind, the rules are applicable to any clinical investigation in humans, including studies of the fruits of biotechnological innovation and the performance on humans of biotechnological experiments. The rules issued by the FDA are complemented by standards issued by professional bodies and by the pharmaceutical industry.

  Comment: While these regulations are as complete and are as conscientiously applied as one will encounter anywhere in the world, some difficulties may be anticipated when a study involves a biomedical intervention or product for which there is no reasonably close precedent. It is hard to explain the possible benefits and the risks to a trial subject when, as may be the case, even experts in the field are in doubt on these matters. One does not as yet encounter clear guidelines on these situations. At the very least it would seem necessary to insist on an appropriate constitution of the institutional review board (to include experts in the specific field of biomedicine), inclusion of relevant measures and of indicators for termination of the study, adequate follow-up to detect late effects, and a generous compensation arrangement for injury.

- *Animal experimentation* – The need for and acceptability of large-scale animal experimentation in order to meet regulatory requirements has been more violently debated in the United States than in most other countries.[45] In its major field of work, *i.e.* evaluation of new drugs, the FDA continues to set extensive requirements regarding animal studies, particular involving chronic toxicity investigations and certain special studies (*e.g.* of carcinogenicity and effects in pregnancy). Much work has been done to find alternative means of pre-clinical testing (*e.g.* in vitro work using biochemical systems) and the volume of animal experimentation is reliably stated to be declining, but the controversy is likely to continue for a long period. Where exploratory innovative work using biotechnological methods is concerned, the current scientific literature seems to show that much may be achieved both by in vitro studies and by small-scale tests on very limited numbers of animals examining highly specific, measurable and reversible responses without the need to sacrifice test animals at all. In the light of current discussion in the United States it seems likely that a partial solution to the controversy regarding animal suffering will be found, and that regulatory requirements regarding safety testing will be modified accordingly. At the moment, however, this conclusion remains speculative.

[45] In many other countries there have of course been major efforts to limit or avoid animal experiments, but these reflect humane considerations rather than regulatory issues.

- *Specific Regulation of Biotechnological Research* – The *NIH Guidelines on the Use of Recombinant DNA Molecules* seek to ensure that laboratory experiments on genetically engineered organisms pose no threat to human safety or the environment.[46] Researchers receiving federal funds must follow the guidelines, which have been widely adopted by the biotechnology research community. Finally, under the National Environmental Policy Act, any researcher who receives federal funds, or whose research is subject to federal regulations, may be required to prepare an environmental assessment to determine whether the research will result in a significant environmental impact.

- *Human and animal drugs and vaccines* – The FDA has long regulated drugs and vaccines for use in human subjects, and the definition of the products falling within its scope is sufficiently broad to include those novel therapeutic or prophylactic products resulting from biotechnological innovation.

  Comment: In the field of regulation of drugs for human use, the US FDA was long regarded as a lead agency providing an example to others. This situation has changed somewhat because of extreme commercial and political pressures on the agency in recent decades, with opponents seeking to limit its authority and scope. Notable was the passage in 1995 of legislation that exempted many thousands of "health products" (curiously entitled "dietary supplements") from the pre-approval requirements of these Agency, though it may intervene when problems arise. The products in question include many of plant origin and the relaxation of the law has resulted in some serious complications.47 Difficulties could therefore arise if such products were to include novel plant materials resulting from biotechnological innovation; post hoc intervention by the agency could then come too late to prevent undesirable complications.

- *Veterinary biologicals* – Under the Virus, Serum, Toxin Act,[48] USDA-APHIS Veterinary Services inspects establishments producing biologicals; the same agency licences veterinary biological substances, including animal vaccines, that are products of biotechnology.

- *Food and animal feed* – The FDA is responsible for ensuring the safety and proper labelling of all plant-derived foods and feeds, including those developed through bioengineering. All foods and feeds, whether imported or domestic and whether derived from crops modified by conventional breeding techniques or by genetic engineering techniques, must meet rigorous safety standards. Under the law it is the responsibility of food and feed manufacturers to ensure that the products they market are safe and properly labelled, and they are liable at law if they fail to meet these standards. There is inspection, but no product-by-product approval process such as applies to medicines; however, any food additive, including one introduced into food

[46] *Federal Register* 34496, amended 59 *Federal Register* 40170, 60 *Federal Register* 20726, 61 *Federal Register* 1482, 61 *Federal Register* 10004. NIH recently revised the structure and role of its Recombinant DNA Advisory Committee with respect to recombinant DNA experiments involving human subjects. 61 *Federal Register* 59725, 22 November 1996. This revision transferred to the FDA the Committee's responsibilities for approving *individual* recombinant DNA experiments involving human gene transfer, while maintaining the Committee's responsibilities for discussion of the general admissibility of novel human gene transfer experiments.

[47] The declassification under the 1994 Act of appetite-depressant plant products derived from *Ephedra,* for example, resulted in serious and sometimes fatal cardiac complications, since neither the selection nor the processing of the plant materials provided for a safe content level of ephedrine and its congeners in certain of the end-products. The FDA found itself obliged to intervene.

[48] Known in full as the Viruses, Serums, Toxins, Antitoxins, and Analogous Products Act (21 U.S.C. 151-159) of 1913, revised in 1985.

or feed by way of plant breeding, must receive FDA approval before marketing. To meet the challenge of foods and feeds derived from genetically engineered crops, the FDA encourages manufacturers engage in a "voluntary consultation process" (essentially a complete product review before marketing); to date, all foods and feeds from genetically engineered crops on the market in the United States have gone through this consultation process.

- *Agricultural products* – The USDA-APHIS regulates organisms and products that are known or suspected "to be plant pests or to pose a plant pest risk" (*i.e.* those that could pose a risk to plant life) including those that have been altered or produced through genetic engineering. These are called "regulated articles". The service regulates the import, handling, interstate movement, and release into the environment of regulated organisms that are products of biotechnology, including organisms still undergoing limited experimental use or field trials. "Regulated articles" are reviewed to ensure that, under the proposed conditions of use, they do not present a plant pest risk, through ensuring appropriate handling, confinement and disposal. The agency evaluates a variety of issues, including the potential for plant pest risk; disease and pest susceptibilities; the expression of gene products, new enzymes, or changes to plant metabolism; "weediness" and impact on sexually compatible plants; agricultural or cultivation practices; effects on non-target organisms; and the potential for gene transfer to other types of organisms. If such an organism or product ultimately appears safe, there is a process by which it can be "deregulated", *i.e.* released for use without further oversight by the USDA-APHIS.

  Comment: While this procedure is in most respects exemplary, one is bound to wonder, from the international point of view, what the consequences could be of "deregulation" of, for example, a modified living organism. Many of the organisms likely to be involved (bacteria, fungi, etc.) are highly mobile and, once deregulated and brought into widespread use, could readily enter territories beyond the United States where their potential to do harm to the local environment might be different, and where one might have wished to regulate, restrict or prohibit them. This inevitably raises the question of whether global rather than purely national control of these matters would not be desirable. Much the same concern must apply to genetic modification of crops, since seeds and seedlings can easily pass national borders, often without human intervention.

- *Pesticides* – These fall under the auspices of the Environmental Protection Agency (EPA), which maintains a regulatory process governing the sale, distribution and use of pesticides in order to protect health and the environment, regardless of how the pesticide was made or its mode of action. This includes regulation of those pesticides that are produced by an organism through techniques of modern biotechnology. A specialised division of the Agency regulates the distribution, sale, use and testing of pesticidal substances produced in plants and microbes. Experimental Use Permits are required for field testing. The agency also sets tolerance limits for residues of pesticides on and in food and animal feed, or establishes an exemption from the requirement for a tolerance, under the relevant legislation; it is clear that this entire procedure will apply to products emerging from biotechnology. The Plant Protection Act of 2000[49] updates and broadens the authority of the agency with respect to pesticides and allied products.

- *"New" microorganisms* – While the Toxic Substances Control Act (TSCA) of 1976 was enacted primarily with dangerous (synthetic) chemicals in mind, the EPA has interpreted the term "chemicals" to include microorganisms. The EPA's TSCA Biotechnology Program of the Office of Prevention and Toxic Substances therefore

[49] The Plant Protection Act, Pub.L. 106-224, Title IV, 114 Stat. 438 (20 June 2000).

regulates microorganisms intended for general industrial and other uses. The programme conducts a pre-market review of "new" microorganisms, *i.e.* those formed by deliberate combinations of genetic material from organisms classified in different taxonomic genera.

Developers must notify the EPA 90 days prior to manufacture or 60 days prior to field testing of a product regulated under the Act.

> *Comment: The broad interpretation put to date on the Toxic Substances Control Act by the implementing agency suggests that there will reasonable control of "novel" microorganisms, whatever their field of use. The notification requirement regarding field studies and manufacturing probably amounts in effect to a regulatory barrier to undesirable studies. It is not, however, clear from the published material how the EPA will be able to deal with risks presented by potentially dangerous microorganisms if these escape from the limited environment within which they are intended to be used. Here again the problem of cross-border dissemination could arise.*

- *Co-ordination of product regulation* – New biotechnology products are, as is evident from the above, essentially regulated under the same statutory and regulatory framework used for other food, drug, animal, plant and chemical products. Since this framework involves several different agencies and has the potential for regulatory overlap and conflict, efforts have long been made within the executive branch to develop an integrated approach to regulating biotechnology products. This approach is reflected in the 1986 Co-ordinated Framework for the Regulation of Biotechnology, which clarifies the areas of responsibility of the various federal agencies.[50]

- *Stem cell research*[51] – Human cord blood stem cells show pluripotent potential and can undergo extensive proliferation. The Stem Cell Therapeutic and Research Act of 2005[52] seeks to make this material available for widespread use, *e.g.* in repairing neurological damage and treating leukaemia.

Overall comment on the US situation – As compared with most other parts of the world, the United States has very broad and generally flexible legislation in the relevant health fields; it has explicit provisions and practices relating to various forms of biotechnological innovation. A number of explicit reservations are however expressed in the individual comment sections above. The long-term effort to co-ordinate the work of the various agencies concerned with biotechnological issues needs to be emulated in other parts of the world.

5.2. The European Community

In view of the close collaboration in matters of health regulation among member states of the European Union (and, for that matter, among the European Union, the United States and Japan), the situation in the European Union as a whole will be considered, with less attention paid to measures taken in individual member states.

- Human experimentation – Directive 2001/20/ECc of the European Parliament and Council of 4 April 2001 governs the implementation of good clinical practice in the conduct of "clinical trials on medicinal products for human use". While the Directive does not apply to non-interventional studies [Art. 1(i))], discussions to date of the

[50] *Coordinated Framework for Regulation of Biotechnology*: Announcement of Policy and Notice for Public Comment, 51 *Federal Register* 23302-23393, Office of Science and Technology Policy, 26 June 1986.
[51] I will not enter here into the ethical issues surrounding the use of stem cells obtained from the human foetus following spontaneous or induced abortion; this is a general ethical issue and not a matter of regulation.
[52] The Stem Cell Therapeutic and Research Act of 2005, Pub. L. 109-129, 119 Stat. 2550.

Directive (and its implementing instruments in member states) do not suggest that its limitation to "medicinal products" would exclude biotechnological experiments in humans. The preamble to the directive explicitly refers to the broadly formulated aims of the 1996 version of the World Medical Association's Declaration of Helsinki. Article 20 provides that the Directive "shall be adapted to take account of scientific and technical progress" which again suggests a broad approach.

- *Animal Experimentation* – Directive 86/609/EEC of 1986 on "the protection of animals used for experimental and other scientific purposes" sets a general framework for animal protection and seeks to encourage the use of alternatives to animal studies, but to date detailed regulation lies with member states. A process of revision has been in motion for a number of years, and will ultimately result in harmonisation and updating of the laws and regulations.
- *Drug law and regulation* – Because of its need to ensure the free movement of goods, the Economic Community was engaged from 1965 onwards in the process of harmonising national laws and policies with respect to drugs for human and animal use. Increasingly intensive procedures with respect to consultation and mutual recognition of regulatory decisions in this field culminated in 1993 in the establishment of a central agency (the EMEA, i.e. European Medicines Evaluation Agency) dealing with drug approval,[53] though to date there is still considerable scope for national decision taking. In broader consultations the European Union engages with the United States and Japan in the work of the International Conference on Harmonisation (ICH), that has developed common policy documents on a range of issues (see separate section below).

- *Biotechnological Policies and Life Sciences*[54] – Since 2002 the European Commission has been formally engaged with the issue of "Life Sciences and Biotechnology", developing strategies in this field and reporting annually on progress. The essential aim is to develop and maintain a progressive strategy, but one of the components is the development of relevant ethical and legal rules.

- *Embryonic stem cells* – In March 2007 the European Commission agreed funding for the creation of a European registry for human embryonic stem cell lines, intended to provide comprehensive information about all human embryonic stem cells lines available in Europe. A publicly accessible Internet site will contain high-quality data on the cell characteristics and relevant developments, including clinical trials.[55]

- *Biodiversity* – In 2007 the European Parliament submitted to the Commission a report on "Halting the Loss of Biodiversity by 2010 – And Beyond: Sustaining Ecosystem Services for Human Well-being". The Commission accepted the report and the view that the maintenance of ecosystem services should become a fundamental goal of all EU horizontal and sectoral policies[56] but to date there does not appear to have been concrete follow-up in the form of directives, though this may be anticipated.

[53] Council Regulation (EEC) No. 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.
[54] A 2004 Report from the Commission to the European Parliament, the Council and the European Economic and Social Committee (Life Sciences and Biotechnology - A Strategy for Europe. Basic document 2002 and annual progress reports 2003-2005).
[55] European Commission Press Release, 4 March 2007.
[56] European Commission Press Release, April 2007.

- *Foods (general)* – The principles of law and regulation regarding food safety remain largely those developed independently in the member states, but a number of common policies have already emerged. In 2002 the European Council adopted Regulation (EC)178/2002 laying down the General Principles and requirements of Food Law, which will lead to increasing harmonisation.[57]

- *GM and novel foods* – Genetically modified (GM) foods and other types of novel foods can only be marketed in the European Union if they have passed a rigorous safety assessment. A "novel food" is defined as a food or food ingredient that does not have a significant history of consumption within the EU before May 1997. All such foods are subject to a pre-market safety assessment under the novel foods regulation (EC) 258 of 1997[58] and Regulation 1829 of 2003 which came into force in April 2004. The safety assessments are carried out by the European Food Safety Authority (EFSA) on a case-by-case basis, and include a detailed consideration of the potential for toxic, nutritional and allergenic effects. GM foods may only be authorised for sale if they are judged not to present a risk to health, not to mislead consumers, and not to be of less nutritional value than the foods they are intended to replace.[59] The need for traceability of GM components features prominently in the regulations.[60] In performing its evaluation, EFSA may consult the authority responsible for food safety assessment in any of the EU member states.

- When an authorisation is requested that includes cultivation of GM crops for feed or food use, EFSA will consult the national competent authorities designated under Directive 2001/18/EC, which deals with the deliberate release of genetically modified organisms. The final decision on authorisation still rests with member states, which vote on each GM food at the Standing Committee on the Food Chain and Animal Health. The European Commission's Register of authorised GM food and feed materials showed as of June 2007 that there had been various authorisations for cultivation of genetically modified cotton, maize, yeast, soya and rape and the restricted marketing of their derivatives in foods or animal feed, but that a number of temporary authorisations in these fields had expired or been withdrawn.

- *Containment of biotechnologically modified organisms* – A Directive of 2001 sets rules regarding the deliberate release of genetically modified organisms into the environment.[61]

5.3. Central and Eastern Europe

With the extension of EU membership into much of Central and Eastern Europe, the pre-EU provisions in these countries are being progressively replaced. It may be noted, however, that most of these countries did have legislation in place relating to biotechnological innovation, with advanced systems in force in Hungary and Czechoslovakia.

[57] Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.
[58] Regulation (EC) No. 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients.
[59] Regulation (EC) No. 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed.
[60] Regulation (EC) No. 1830/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms, and amending Directive 2001/18/EC.
[61] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms.

It may also be noted that in Russia a Federal Act of the Russian Federation on State Regulation of Genetic Engineering was passed as early as 1996. The law establishes fundamental standards regarding the safe conduct of genetic engineering. It does not set up a separate regime of regulation but rather makes provision that biotechnological products should be subject to regular national laws governing health and safety. New Russian legislation requiring the approval and labelling of all food products containing genetically modified materials came into force later.

5.4. Norway

As a non-EU European state, Norway continues to pursue a largely independent course in health policy, though it is obliged by the EEA (European Economic Area) agreements to adhere to some basic instruments of the European Union. The EEA agreements do not extend to the agricultural sector, and in that respect Norway has tended to introduce and maintain more stringent rules than those in force in the Union.

GM foods and plants – Early in 2001, Norway refused to approve three genetically modified food-related products that had been approved by the EU; the products concerned were two types of rape seed oil and a test material to determine whether milk contained antibiotics. The Minister for the Environment based the ban on evidence that GM products could render humans and animals resistant to antibiotic therapy. Norway did grant approval to three genetically modified carnations that were not intended as foodstuffs; since they could not grow in the Norwegian climate, however, the approval was purely a formality.

It seems clear that strong public opposition underlay the Norwegian policy. When the Norwegian National Veterinary Institute conducted a comparative study of opinions in Norway, Italy and the United Kingdom on GM issues, the response in all three countries was similar, but with Norwegian participants showing a particular trust in the national government in the relevant policy issues and indifference as regards the views of the European Union. Most of those questioned considered that food labels should state if the food or ingredients thereof had been genetically modified, that processed food derived from GM crops should be labelled, and that GM and non-GM crops should be kept separate at all stages of processing. In particular, people thought that even foods containing GM ingredients through accidental contamination during processing should be labelled. This implies that effective traceability would be tacitly approved by consumers as a prerequisite of such labelling strategy. At the present time there are no genetically modified (GM) whole foods on the market in Norway, although (as in the European Union) foods on sale may to a limited extent contain genetically modified ingredients.

Biotechnology and human subjects – Norway has in recent years had no significant research-based pharmaceutical industry, but biotechnology is developing; there are some 90 independent biotechnology firms though most are small compared with those existing elsewhere.[62] Significant successes have been reported at the University of Oslo in cellular signalling, which is thought to provide a key to understanding the means by which cellular processes can be governed and modified.

The Norwegian legal provisions regarding human applications of biotechnology are as liberal as those in force anywhere. As early as 1994 a law was passed to make formal provision for the medical use of biotechnology as well as artificial fertilisation and research on fertilised human ova. On 25 March 2007, the Norwegian Parliament passed a revised and more explicit version of this law that includes clearer provisions on the study of human embryos. The legislation permits research on "superfluous" human embryos as well as genetic examination of fertilised human ova before implantation into the uterus ("pre-implantation diagnostics").

[62] See OECD Biotechnology Statistics 2006. See also: van der Molen S and Enzing C: Biopolis Report (Norway), March 2007.

The Act also opens the possibility of creating individuals who can serve as donors of healthy tissue to others in need of it. Research on living individuals must be approved by regional ethical committees, and the Ministry of Social Affairs and Health will be kept informed on all biotechnological work involving human subjects. Although during the Parliamentary debate the Bill was condemned by some political groupings as representing a breach of human rights, there seems little doubt that it will be applied in medical practice.

5.5. Australia and New Zealand

Australia, working in part together with New Zealand, has introduced particularly strict regulation of biotechnology, especially when it is involved in the production of crops and food.[63] The *Office of the Gene Technology Regulator* (OGTR) regulates the use of genetically modified organisms (GMOs) and *Food Standards Australia New Zealand* is responsible for the regulation of food, including food produced using gene technology.

The OGTR is authorised to take decisions on matters regarding genetically modified organisms, including research, manufacture, production, experimental trials, commercial release and importation. It has responsibility for identifying, assessing and managing potential risks to human health and safety and the environment. The Regulator will not issue a licence for any of the activities within their field of competence unless there are sufficient guarantees on these matters. The relevant provisions are backed by the criminal law.

> *Comment: It is not entirely clear where the borderline lies between "commercial release", which is at the discretion of the Regulator, and "marketability and agricultural trade issues", which are the responsibility of other bodies, including State and Territory governments.*

Food Standards Australia New Zealand (FSANZ) ensures the safety of all consumable foods, including imports, and is concerned with these products at all stages, from primary production through to manufactured food and food retail outlets. As of April 2004, FSANZ had approved 23 GM food commodities, which consist of varieties of GM corn, cotton (a source of cottonseed oil), rapeseed (canola), sugar beet, soy and potato.

A standard for labelling GM food has been in force since 2001. It requires any food, food ingredient or processing aid produced using gene technology and containing novel DNA or novel protein to be labelled as "genetically modified". The standard also allows 1% unintentional presence of GM food or ingredient in a final food.

Public consultation features prominently in the Australian biotechnology and gene technology regulatory system, relating both to proposed regulations and to decisions by the agencies concerned. The OGTR website provides ongoing information on all GM products approved by the regulator, by Food Standards Australia New Zealand or by the Therapeutic Goods Administration (*i.e.* the Drug Regulatory Agency).

Other relevant legislation and regulation at the Federal level in Australia[64] includes:

- The Gene Technology Act No. 169 of 2000.
- The Prohibition of Human Cloning for Reproduction Act 2002.
- Research Involving Human Embryos Act 2002.
- The Environment Protection and Biodiversity Conservation Act 1999.

[63] It has been suggested that, following the change of government in Australia in December 2007, the severe restrictions with respect to genetically modified crops and foods may be relaxed. However, the influence of political change in such a field is difficult to predict; a left-wing government may be even more prone to restrict innovations perceived as primarily serving an industrial interest.

[64] Handbook on the Regulation of Gene Technology in Australia; Government of Australia, 2002 and updates.

5.6. Korea

In 2001, the Korean Bioethics Advisory Commission (KBAC), sponsored by the Ministry of Science and Technology, published a set of recommendations for biotechnological research and application, including scientific experiments with human embryos. The issue has remained controversial. In 2002, the government approved a draft for a bill that would prohibit human cloning and imposed severe penalties on offenders; passage of the bill through the legislature however stagnated. In 2004 a major scandal occurred relating to claims advanced that year by the Korean investigator Hwang Woo Suk regarding the successful cloning of human embryos as a step forward in therapeutic and pathogenetic research; both the technical merits and the ethics of the work were subsequently seriously challenged,[65] and the investigator later admitted that his work was largely falsified. As of early 2008 it seems likely that the dormant legislation will be revised and completed, but it remains uncertain what its ultimate form and content will be, particularly since in September 2007 the authorities appeared to be moving towards licensing some degree of human cloning.

5.7. India

In view of the size and diversity of the Indian pharmaceutical industry and its importance to the growing economy, one might expect to find significant advances in the development of regulation to meet the changing situation. There is in fact very little evidence of such a development. The regulation of drugs in India has been bedevilled by inefficiency on the one hand and a far reaching delegation of responsibility to the States on the other. The result has been a failure to guide or control the market in the interests of public health. Overprescribing is extremely common, and the few reputable manufacturers of medicines are heavily outnumbered by small firms of poor standard, commonly engaging in counterfeiting and other forms of fraud.[66] This being so, it would be too much to look to India at present for a lead into any form of pioneering development where regulation is concerned. The situation contrasts with the extensive involvement of the (Federal) Ministry of Science and Technology in the promotion of biotechnological research and the exploitation of its output.[67] This Ministry proves to be well aware of the risks to health involved in biotechnological work, has issued a series of guidelines to contain them,[68] and has been involved in the approval for marketing of biotechnological insulin, GM-CSF, G-CSF, interferon alpha, interferon gamma, interleukin, Blood Factor VIII, streptokinase, HBsAg vaccine, human growth hormone, tPA, erythropoietin, follicle stimulating hormone and human protein C, and approval of at least five such products for national manufacturing. This could represent a useful structure for future progress, with Ministries of Health and Ministries of Science working together in this field.

5.8. China

There are good reasons to anticipate that China will in due course acquire a prominent and perhaps a leading position in health-oriented biotechnological research, and probably also in the development of appropriate regulation. The positive developments have unhappily been counterbalanced in recent months by a series of serious problems.

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[65] Human Cloning and Scientific Corruption: The South Korea Scandal and the Future of the Stem Cell Debate. *The New Atlantis*, Number 11, Winter 2006, pp. 113-117.

[66] The present writer examined the situation in one Indian State for the World Bank; the State Inspectorate routinely inspected four drug manufacturing plants of fair but not distinguished standing. However, due enquiry in the principal city showed that eight other firms existed, none of which was registered with the inspectorate.

[67] Website of the Department o**f** Biotechnology, Ministry of Science and Technology, Government of India; updated 26 November 2007.

[68] *E.g.* Rules Regarding the Manufacture, Use, Import, Export and Storage of Hazardous Micro-Organisms, Genetically Engineered Organisms or Cells, New Delhi, 1989 (with later updates accessible via the Internet).

The *positive* side of the picture reflects the manner in which China has in the course of a relatively short period developed a thriving pharmaceutical industry with a flourishing export trade, and seen the establishment of a large number of biotechnological firms with research ambitions. A national policy on biotechnological development has been created, state research centres set up in six cities (some collaborating closely with Western research firms) and biotech parks have been designated.[69,70] High priority is being accorded to investigating and developing genomic drugs and vaccines, including products aimed at cancer, hepatitis and AIDS, while stem cell research is progressing rapidly.[71] A number of foreign and domestic biotech products have been registered, and in some cases foreign manufacturers have found it possible and attractive to arrange for manufacturing in China. According to official statements, 21 recombinant pharmaceuticals, including interferon, insulin and GCSF,[72] have been commercialised in China since 1993.

The *negative* side of the situation relates to the discovery that China has become a major source of counterfeit drugs, reaching many other countries, and that there has been massive corruption in the drug regulatory field. These matters have given rise to international concern but also to public unrest in China itself. The head of the Drug Regulatory Agency (the Agency for Registration of Medicinal and Health Care Products) was tried and executed for corruption in 2007.

What all this means is that before true progress can be made in regulation for the future, some fundamental correction is necessary in the existing system. Because the situation was so serious, rapid action has been taken.[73] Following the death of ten people from the use of a locally made antibiotic, a programme was set up in 2007 to review the production licences for some 170 000 medicines;[74] a proportion have already been found to be defective.[75] The national inspectorate has created a fleet of 400 travelling laboratories to detect falsification and counterfeiting. An entirely new regulatory system is in development and will be in place by 2010; already the time needed for assessment of new drug applications has been reduced to something resembling the European norm of 90-120 days. An agreement was concluded in December 2007 with the United States FDA for the exchange of certain regulatory information. For the moment, however, there is no specific provision for the assessment of biotechnological health products, nor is there a well-defined fast-track system for applications of any type. All the same, the revamped Agency is showing its teeth: in December 2007 it brought about the recall of 100 000 vials of a Merck (US) vaccine that was found to be contaminated.[76]

In the meantime, the market continues to develop apace, as does research.[77] GlaxoSmithKline (UK/US) will invest USD 100 million by late 2008 at the Shanghai biotech R&D centre, employing 1 000 staff there by 2010 with the primary intention of developing new agents for biodegenerative conditions. Apligraf, a US-developed regenerative medicinal product based on human dermal cells, is now to be sold through China to the whole of Asia and will be made locally; the American Healive vaccine for hepatitis A has been approved for sale. These examples point to the development of close and trusted contacts between Chinese and foreign firms and authorities.

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[69] Website Austrade (Canberra), 20 November 2007.
[70] Glaser V. (2007): China Expanding Bioresearch Activities. Genet. Engineer. *Biothech. Nws,* 27(28), 25 October.
[71] Salter B, Cooper M and Dickins M (2007): China and the Global Stem Cell Bioeconomy: An Emerging Political Strategy? *Regenerative Medicine*, 1(5): 671-683.
[72] Granulocyte Colony Stimulating Factor.
[73] Anon. (2007): China Pharmaeutical Regulatory Report 2007. Pacific Bridge Medical, Bethesda Md.
[74] Anon. (2007): Chinese Researcher Helped Shake Up Corrupt Drug Agency, *Fierce Biotech* (website), 4 April.
[75] Anon. (2007): China Biotech Week in Review: Safety Regulation Improves. *China Bio Today* (website): 16 December.
[76] Innform (website), 18 December 2007.
[77] Anon. (2007): *Drug Development Opportunities in China.* Business Insights, New York, September.

No doubt the current transitional phase will pass rapidly, but so long as it persists China will be faced with some problems reflecting its culture and ambitions as much as its technical needs:

> The ministry has had to grapple with two principal questions. Is regulation in China necessary – or even desirable? And if it is, should guidelines be based on Chinese cultural characteristics like Confucian principles, or on the international guidelines that have been mostly developed by western ethicists? Some scientists have advocated the development of biomedical research and biotechnology without constraint – arguing that such freedom will allow China to more rapidly catch up with efforts in developed nations.[78]

A final note must be added on the issue of biogenerics, *i.e.* generic equivalents of original biotechnology products. As noted in Section 4.9 of this report, this is a complex and developing field and the rules of play are still unclear. China has a considerable biogenerics industry and it is very alert to the need for some measure of protection of intellectual property rights, whether through patents or regulatory rules, particular since its loss to western firms of the rights to the traditional Chinese medicine artemisinin.[79] It is likely that in this area China will be in the forefront of rulemaking.

5.9. Interregional agreements

As noted above, the International Conference on Harmonisation, involving the European Union, Japan and the United States, has developed a large number of harmonised standards relating to drug regulation. Its products relative to the present topic comprise to date:

S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Q5E: Comparability of Biotechnological/Biological Products subject to changes in their manufacturing

Q5D: Quality of Biotechnological/Biological Prod.: Derivation and Characterisation of Cell Substrate

Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

Q5B: Analysis of the Expression Construct in Cells Used for Production of r-DNA (Biotechnological)

Q5A(R1): Viral Safety Evaluation of Biotechnology Products

Examination of these documents (or of the guidance documents for industry which participating states have derived from them) is informative particularly as regards the *range of products* to which they apply and the *methods recommended for study*.

The *range* of products or substances is very broadly defined and foresees further extension as knowledge expands. The rules are intended to apply to "products derived from characterised cells through the use of a variety of expression systems, including bacteria, yeast, insect, plant and mammalian cells"; the substances covered include "proteins and peptides, their derivatives and products of which they are components", and they may have been derived

[78] Qui Rebzong (2007): China's New Bioethics Regulations Will Protect Human Species While Allowing Biomedicine and Biotechnologies to Develop. SciDev.Net (website): 18 May.
[79] Yibing Zhou E. (2007): *Advances in Biopharmaceutical Technology in China.* Society for Industrial Microbiology and BioPlan Associates.

from cell cultures or produced using recombinant gene technology. The purposes of preclinical evaluation are declared to comprise:

(1) The identification of an initial safe dose for humans and subsequent dose escalation schemes.

(2) Identification of potential target organs for toxicity and to determine whether such toxicity is reversible.

(3) Identification of safety parameters for clinical monitoring.

This approach is in accordance with current thinking on animal studies in general. It appears to shift the main burden of proving safety onto studies in man, the animal work only serving to indicate what needs to be studied in humans and how. There is also a welcome reference to studies on isolated materials (notably in vitro work). On the other hand, when any of the evidence obtained suggests a possible form of toxicity or noxious effect, the relevant document hastens to point to the need to follow this up with more traditional studies, including long-term toxicity or carcinogenicity studies, as appropriate. These documents point to the possibility that materials derived from living tissue may be contaminated with noxious substances, and underline the need for progressive purification. The texts stress that "conventional approaches to toxicity testing of pharmaceuticals may not be appropriate for biopharmaceuticals" due to such factors as "species specificity, immunogenicity and unpredicted apheliotropic activities" and note, for example, that high-dose toxicity studies or carcinogenicity studies may be unhelpful in the case of such products. The need to exclude viral contamination is stressed. By and large, however, these documents do not succeed in providing very specific guidance as to what needs to be done, other than stressing the need for caution and flexibility, adapting one's methods from one type of substance to the next. Overall, the ICH documents, drawn up by regulators of varying plumage and with input from industrial scientists and policy makers, do breathe the spirit of compromise. In the present state of knowledge, this seems understandable.

5.10. Significant global agreements

- *The United Nations Convention on Biological Diversity*, one of the main products of the 1992 Rio Earth Summit, aims to ensure the conservation of biodiversity (*i.e.* the complete variety of life on Earth), its sustainable use, and the fair and equitable sharing of the benefits arising from the use of genetic resources. The Convention thus has a potentially huge impact, but relies heavily on action at the national level and under other related treaties and in other international forums to achieve its objectives.

- *The International Treaty on Plant Genetic Resources for Food and Agriculture* entered into force in June 2004 with its ratification by 55 countries. It is primarily designed to ensure the maintenance of biological diversity in crops.

6. Regulation of health products in selected biotechnological fields

It is argued elsewhere in this report that views on the future pattern of regulation of biotechnological health products are to some extent unavoidably speculative, since the future of technical and medical developments in this field cannot be foreseen and surprises are inevitable. The brief sections that follow do, however, attempt to present some views on what may and perhaps should happen in a number of areas in which the ongoing OECD study has expressed particular interest.

6.1. Vaccines

Vaccines of all types are already regulated in almost every country either under drug law, or special provisions relating to vaccines and immunological agents. New types of vaccines developed through biotechnological research will automatically fall under these provisions, subject to whatever general new measures are found to be necessary to handle biotechnological products in general. Some special concerns of vaccine law relate to:

a. The possibility that the vaccine may in some cases induce the very condition that it is intended to prevent; there has to be evidence that this risk has been reduced to negligible proportions or entirely excluded. ¨

b. The presence in some vaccines of animal protein or other foreign materials that could cause hypersensitivity reactions (*e.g.* anaphylaxis). It is likely that this problem will be eliminated entirely when using certain biotechnologically produced vaccines without involving animals.

c. The possibility that a superficially administered vaccine (scratch immunisation) may by cross-contamination affect individuals other than the vaccinee.

6.2. Therapeutic agents and invasive diagnostics

These fall under existing drug law and will be subject to its provisions.

6.3. Gene Therapies[80,81,82,83]

Gene therapy is a technique for correcting defective genes responsible for disease development. It can in principle be used both in hereditary conditions and in malignancies. Several approaches are possible. a normal gene may be inserted into a non-specific location within the genome to replace a non-functional gene – this approach is the most common. Alternatively, an abnormal gene could be swapped for a normal gene through homologous recombination. It may also prove possible to repair an abnormal gene through selective reverse mutation, which returns the gene to its normal function, or to alter the "regulation" of a particular gene, *i.e.* the degree to which it is turned on or off. In experimental work to date, the gene is attached to a "carrier" or "vector" (usually a virus, because of the ability of such an organism to enter the cells), though modified DNA might be administered directly into the tissues without using a vector. In some promising work, re-engineered lymphocytes have been used to attack malignant cells in patients with advanced metastatic cancers, while elsewhere liposomes with a protective coating have been used as carriers.

Progress in this field to date has been impeded by reports of some severe and even fatal reactions in experimental clinical work in France and elsewhere. In one case there appears to have been a severe immune response to an adenovirus vector; in another an unexplained leukaemia-like condition occurred. For a time, the United States FDA prohibited all further clinical work in this area.

The *risks* of gene therapy are still incompletely defined: some relate to the viral or other vector that may be introduced into the system; others remain unexplained. The *efficacy* of gene therapy promises to be dramatic in some hitherto untreatable conditions with a poor

[80] Anon. Oak Ridge National Laboratory (2007): *Gene Therapy.* Website of the Human Genome Programme of the US Department of Energy Office of Science, Office of Biological and Environmental Research. Consulted 16 November.
[81] Anon. (2007): Gene Therapy – An Overview. *Biotechnology in Perspective.* Biotechnology Industry Organization, Washington DC.
[82] Anon (2007): *Gene Therapy – Molecular Bandage?* University of Utah, Genetic Science Learning Center.
[83] Anon (2007): Gene Therapy Clinical Trials Worldwide. *Journal of Gene Medicine*, London. Updated July 2007.

prognosis, though the duration of efficacy may prove to be a problem; with the rapid multiplication of cells it is not at all certain that a genetic correction introduced at one point in time will be maintained. In both respects the fact that one is dealing with a costly and potentially dangerous therapy, often intended for extremely rare conditions, means that conclusions may have to be based on very limited human experimental data, but where such a treatment appears to bear great promise in hitherto hopeless situations there is likely to be a considerable acceptance of risk.

Gene therapy is not specifically covered in the task descriptions of most regulatory agencies, but it would seem to fall logically under both drug regulation and provisions regarding clinical trials. Since the responsibilities of the United States FDA are broadly defined, extending to biological products and including the licensing of experimental treatments, it has already been able to act in this field. Not all regulatory agencies in other countries have such a broad competence and their authority may need to be extended to cover this area, with the specific task delegated to specialised subcommittees.[84]

6.4. Tissue Engineering[85,86]

Tissue engineering ("regenerative medicine") has been well defined by the US National Institutes of Health as "an emerging multidisciplinary field involving biology, medicine, and engineering". It comprises a series of different approaches that include the use of stem cells and genetically engineered cells, the development of novel biomaterials designed to direct the organisation and differentiation of cells, use of growth factors and agents governing vascularisation, and the development of biocompatible materials for repair purposes, derived either from chemical synthesis or transgenic plants and animals. The plastic-based bone substitute ostamer, noted earlier in this report, was a very early but unsuccessful venture.

Some of the approaches in this field are closely analogous to those covered by references in drug law to "substances affecting physiological function", and bring them within the scope of that field of law. Others (involving the use of biocompatible materials) are in effect a form of surgery, a field in which government authorities have generally been reluctant to become involved, regarding it as a purely professional matter. Bodies governing the medical and surgical professions, often as a form of self-regulation, have set certain standards (*e.g.* for ethics in experimental surgery), but not consistently. The *risks* of innovation in this field are still poorly defined, but in opinions voiced to the present writer they are described as relating primarily to acute reactions (rejection, anaphylaxis) or to a derailment of normal cell function to the point where malignant or other forms of degeneration are induced.

As in a number of other biotechnological areas, there would seem to be good reason to bring this matter within the scope of health and drug regulation87 and the governance of clinical trials, so as to ensure the development of sound evidence and responsible assessment of the efficacy/safety ratio prior to general adoption.

[84] In the United Kingdom, the Gene Therapy Advisory Committee GTAC is the national research ethics committee (REC) for clinical studies of gene therapy under the Medicines for Human Use (Clinical Trials) Regulations of 2004; it is the only body empowered to approve clinical trials of gene therapy products.
[85] McIntire LV *et al.* (2002): *WTEC Panel Report on Tissue Engineering*. World Technology Evaluation Center, College Park, Md.
[86] See *inter alia* the informative website of the UK Centre for Tissue Engineering, Liverpool and Manchester.
[87] In the United States, tissue engineering has been brought within the scope of the regulations relating to medical devices. See http://www.fda.gov/cdrh/index.html, and in particular the section of the latter dealing with Tissue Engineered Medical Products Standards.

6.5. Non-invasive diagnostics[88]

Diagnostic agents not intended for administration to the subject clearly present no physical risk. There is however a need to ensure that they are reasonably reliable, especially in view of the possibility that an incorrect positive diagnosis will have adverse psychological effects while an incorrect negative diagnosis is likely to result in failure to provide necessary treatment, *e.g.* in cases of a serious contagious disease. It is true that many non-invasive diagnostics have (since 1968, when the first *in vitro* pregnancy tests were marketed) been introduced without any need for formal approval but it is arguable that there is a need for something more than the ordinary rules relating to commercial products and the veracity of advertising claims.

6.6. "Nutraceuticals"[89]

This curious concept was discussed briefly in Section 4.11. So long as the term has a purely commercial function without a consistent scientific basis it is not possible to consider the need for regulation. Some products described as "nutraceuticals" or "fortified foods" are in effect orthodox foods enriched by the addition of (generally unnecessary) supplementary nutrients and their acceptability is a matter for food law. The primary question here is one of possible misinformation and overcharging, and the extent to which society should tolerate a certain level of commercial hyperbole. The term has also been used for ordinary foods (red wine, soya flour) when certain health benefits of these are elucidated, and for traditional herbal tonics such as ginseng. The appellation "nutraceutical" has further been applied to nutrients having a pharmaceutical form (generally vitamin or mineral supplements presented as tablets or capsules); whether these fall under drug law or food law relates in most countries to the presence or absence of medicinal claims and the dosage level provided. It should be realised that vitamins and minerals in overdose are not harmless.

As noted earlier, it is in theory possible that synthetic "super-nutrients" might be developed capable of boosting or supporting health in a manner unattainable with traditional foods; in that case the term "nutraceutical" might have a useful function. Until now it does not. \

7. Discussion: Current situation and the need for further development

7.1. Progress and impediments to date

Any overview of the current and developing state of biotechnology and its regulation as a public health issue is unavoidably speculative to some extent. The technology itself is diverse and developing fast; the risks that it might present are not fully known; the relevant regulations have not yet been fully tested in these matters. There is obviously a need for ongoing watchfulness and adaptation in a field that may by 2030 have changed considerably. All during the time to then the public health consequences of these developments are likely to remain a subject of discussion and even sharp controversy. The latter is not exclusively (and perhaps not even predominantly) scientific in nature: important commercial, political and sometimes religious elements (as in the case of stem cells from the aborted foetus) enter into the debate.

[88] Note: the Special Programme for Research and Training in Tropical Diseases (TDR) sponsored by UNICEF, UNDP, the World Bank and the World Health Organization completed a global survey of diagnostics regulation in 2001. Based on this survey the programme published its report *Regulation of in vitro Diagnostics: A Global Perspective* in 2003.

[89] The current Wikipedia text provides a good summary of the various and divergent ways in which the term "nutraceuticals" has been employed.

The hypothesis developed at the outset of this paper, *i.e.* that certain of the forms of health regulation already in existence can with appropriate interpretation suffice to deal with most biotechnological novelties, appears to be correct, but with a number of reservations.

a. Firstly, the growing importance of biotechnology to the health field creates a need for *some supplementary provisions in law, sometimes entailing the creation of specialised institutions*. The latter are well exemplified by the regulations in force in Australasia and the role there of the Office of the Gene Technology Regulator (OGTR). Such complementary provisions are required in fields, such as that of gene technology, that demand particular knowledge and experience in order to assess and decide on relevant issues. These new institutions need to work in close collaboration with existing regulatory bodies (*e.g.* those handling drugs and foods) in order to ensure a watertight system and consistent operation.

b. Within existing regulatory systems *particular flexibility will be called for in applying existing rules*. The Ethical Review Body that is called upon to assess the acceptability of a proposed human experiment, and that is generally supposed to have insight into the risks posed by chemical drugs and means of predicting them, will for example need to be differently constituted if it is to consider the acceptability of a biotechnological experiment in humans. Similarly, decisions by requirements set or implemented by drug regulatory bodies regarding preclinical work will need to be interpreted and sometimes modified where biotechnological innovations are concerned. A novel agent administered on a single occasion to exert an acute effect, modifying the functioning of a biological system, will probably not need to be the subject of chronic toxicity studies in animals, but both in animals and in man long-term follow up of the consequences of the change will be necessary. The regulatory provisions in operation to prevent excessive suffering in animal experiments may need some rethinking where genetic experiments rather than toxic chemicals are concerned. All these things should be possible in view of the flexibility of the established national systems of regulation, but the need for adaptation must not be overlooked.

c. It seems very likely that *on some matters of global significance, where an innovation, once introduced, cannot be contained within national borders, international decision making will be called for*. An example cited in Section 5 related to the authority accorded to a US agency to "deregulate" a particular innovation once safety has been demonstrated to its satisfaction. If the innovation relates to a seed or spore, however, its dissemination may very soon have repercussions in other countries and environments. The ICH has laid a promising basis for joint action by major countries, and the global agreements cited in this report reflect a wide understanding of the need to act consistently across borders.

d. Conversely, the fact that on some of these matters a national body has traditionally been obliged to *delegate certain decision-making powers to provisional or local bodies* may need to be reviewed (see discussion on Australia in Section 5), bearing in mind the perhaps limited ability of such bodies to pass judgement on biotechnologically novel issues.

e. Much like the case where drugs are concerned, *small and developing countries may not possess the resources and experience* needed to deal with these new technical issues on behalf of their own populations. This could provide a further argument for global or at least regional decision making (see "c" above), or for mutual recognition of decisions under a global convention.

f. The desirability of adequate and formalised routines for *public consultation, e.g.* as existing in Australia, seems clear.[90] The general public has been alternately reassured and alarmed by information regarding biotechnological innovation. There is an awareness that considerable commercial pressures can be exerted in this field (*e.g.* as regards GM crops) and there is sometimes a degree of mistrust of scientific institutions.[91]

g. The *regulation of biogenetic testing facilities merits attention.* Where biogenetic testing is purely a topic of academic or institutional research there would appear to be no overall need to regulate it, though the institution concerned will be bound by generally applicable norms (*e.g.* on animal experiments). The need for accreditation or regulation of an institution is much more likely to arise where such an organisation provides services in this field on which others will rely. An increasing number of commercial laboratories do provide such services, either nationally or internationally, against payment. It is possible for such a unit to seek and obtain ISO accreditation for this activity, providing there is some assurance that the work is being performed to an adequate standard – but certain countries have instituted their own forms of recognition and may apply more rigorous criteria. New Zealand, for example, through a unit within its Ministry of Agriculture and Forestry, has a system of accreditation that *inter alia* examines the standards maintained by domestic or foreign laboratories testing GM seeds or other plant materials that are to be brought into the country. In 2004, following a periodic site audit, New Zealand suspended its recognition of a well-known US laboratory in South Dakota providing services for plant and animal material in this area, despite the fact that the laboratory concerned had ISO accreditation; the Ministry maintained its recognition of certain other laboratories of this type (notably in Australia, the United States and France).

h. *Direct to consumer advertising of medicines* is a disputed issue; it is permitted in the United States and New Zealand (and tolerated in some developing countries) but was rejected by the European Parliament (though the Commission has now sought to reopen the issue). In Canada, where direct to consumer advertising is not permitted, a legal challenge to the prohibition has been raised. A globally uniform approach currently seems unlikely.
Public advertising of biotechnologically derived products used in medicine would similarly be likely to fall under the existing national rules, such as they are, relating to medicines. Direct to consumer advertising of *diagnostic services* has traditionally been regarded as inadmissible, but it has become tolerated to some extent in a number of European countries, certainly as regards diagnosis of pregnancy and paternity. In view of the legal and psychological importance of diagnostic findings in such matters, there would seem to be a need for some uniformity in advertising diagnostic services, perhaps coupled to a licensing system for the provision of such services.

i. <u>*Regulation of gene therapy in medicine*</u> – gene therapy, in the sense of the insertion of genes into an individual's cells and tissues to treat a disease or correct a hereditary condition, appears to fall clearly within the field of activity reserved for the medical

[90] It may be noted that Article 23 of the Cartagena Protocol of 2000 requires public involvement in the decision-making process.

[91] The attempts made by the Rowatt Institute in Scotland in 1999 to suppress the results of a study apparently showing adverse effects of GM potatoes on experimental rats gave rise to much controversy and, rightly or wrongly, was one of the incidents underlying public rejection of biotechnologically inspired foods in Europe. For an overview (not necessarily unbiased) of this case, see: Potatoes Genetically Modified to produce *Galanthus nivalis* Lectin. In: 1999 *Annual Report of the Committees on Toxicity, Mutagencitiy Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.* Department of Health, London, 1999. Much publicity also surrounded the "tomato puree" case: in July 1999, because of public concern, a UK supermarket chain withdraw a tinned tomato puree product that was prepared from US-grown GM fruit, and that had been on sale in the United Kingdom for only six months.

profession. What currently seems to be lacking in existing systems of medical licensing, however, is a definition of the specialisation or special qualifications required in order to undertake this particular type of treatment. This could and should be incorporated into medical practice law.

j. *Tissue engineering* has been defined as the use of a combination of cells, engineering and materials methods, and suitable biochemical and physio-chemical factors to improve or replace biological functions. This has become an important research field but has not so far reached the point of practical application. Once it does so, it would (as is the case with gene therapy) appear to fall under the professional medical licensing system, requiring a definition of the specific training and specialisation needed to treat patients with these methods, while rules regarding the technology itself are likely to be governed by the regulations on medical devices (see Section 6.4).

k. *Priority review systems:* As noted above, the system of drug regulation in the United States had by 1980 become subject to severe delays, and correction was called for. One of the responses was the institution of a system by which individual new drug applications could be accorded a particular level of priority depending on their apparent therapeutic importance. In much of Europe, by contrast, drugs had (as noted above) been assessed according to a legally imposed timetable and few serious delays occurred; no formal system of priorities was therefore considered to be needed. It has now been suggested that a system of priorities should be introduced for new therapeutic and other products of biotechnological origin because of their potential importance. It indeed seems possible that some highly novel products of this type might be subject to regulatory delay because of general overburdening of the system, or because of their unfamiliar character and potential; should this occur it could be necessary to institute a priority grading system in all agencies to ensure that sufficient capacity is mobilised to deal promptly with those products bearing particular promise. However, just as the long familiar field of synthetic chemical drugs has produced, alongside genuine advances, many insignificant innovations marketed primarily for commercial reasons, so biotechnological products are likely to vary greatly in their importance. Where priorities need to be determined the prime consideration must continue to be the likely significance to medicine and human health; a new product must not be accorded preferential treatment merely because it is of biotechnological origin.

l. *Transparency:* As noted in this report, there is now an increasing movement to insist on transparency in fields such as clinical trials and the registration of drugs. The arguments for openness apply with even greater force to the relatively new field of biotechnology, which in many areas seems to bear much promise but may also entail unanticipated risk. Full transparency would entail at the very least the prompt publication (or public deposition) of information on the performance and outcome of clinical trials with products in this area, experimental data pointing to any form of risk, regulatory deliberations, and information on environmental contamination. One might note that industrial firms have often battled transparency because of the fear of revealing industrial secrets, but legislation on intellectual property should be capable of providing reassurance in this regard. Regulatory agencies, for their part, have been loath to reveal data on their acts and motivations because of confidentiality clauses in the law governing their operation. These clauses have sometimes been over-interpreted but they may also need to be reviewed. Much public injury can be avoided if information relevant to emergent risk is made available promptly.

m. *Use of consultation and voluntary codes:* In a number of countries, standards in the fields of food, medicines and other products have not only been the subject of

consultation between the authorities and industry, but have also been formulated by both parties as legal norms and as voluntary codes of behaviour respectively, the two types of instrument complementing one another. This example should be widely emulated in the field of biotechnological products. The active involvement of trade and industry in the development of standards enriches the input to the debate but also generates adherence by industry to the standards that emerge.

n. *Environmental concerns:* The extent to which the possible health risks of biotechnological work have been appreciated and have been reflected in the creation of appropriate regulatory standards still varies markedly from country to country. Since whatever problems arise are likely to be of global significance, broad international consensus should be sought on the steps necessary to avoid unnecessary risks to human health.

7.2. Are there fields not in need of regulation?

Reviewing the vast number of fields of biotechnological activity, it would be overbold at this stage to list any that do not need to be regulated at all. The overriding principle must however surely be that pure scientific exploration should enjoy the maximum of freedom, and that a reasonable degree of protection should be accorded to the successful explorer's findings. Regulation at this stage should be limited to the application of the Hippocratean principle – *primum non nocere* – above all, do no harm. That means essentially that researchers must do no unreasonable or unnecessary harm to their test subjects (whether human or animal) or to the environment. Ethical or religious considerations may interpret this rather more broadly, for example by rejecting the use of human germinal or foetal material. As noted earlier in this report, a non-invasive diagnostic agent need not be regulated as regards safety, but it is fair to argue that it should be reasonably efficacious.

Beyond this, regulation is more likely to be called for as regards the *exploitation* of the scientist's work, for commercial or other ends. Here too, the principle of allowing the maximum possible freedom is surely basic. The nascent but growing "Pharmageddon" movement,[92] though active in formulating public concern regarding the growing potential of medicine (and medicines) to do harm, does not reject that basic principle of freedom in medicine, but expresses concern primarily as regards the manipulation of health care by commercial interests. Regulation, as it has grown up in the last half-century, has indeed not sought to fetter the physician but to protect both the practitioner and the public from the improper application of knowledge.

Surveying once more the extensive listing of biotechnological methods and outputs cited in Section 2 of this report, one is tempted to identify a number which seem highly unlikely to present any threat to human health and well-being. Bearing in mind however a number of medicinal promises from the past that went most fearfully awry, it seems better to resist the temptation. One need not be pessimistic, but one must remain watchful.

7.3. The near and more distant future

In a series of recent papers on the regulation of biotechnology, and in particular genetic modification of food sources, Kinderlerer has taken a balanced but not uncritical approach to regulation in this field. He points out that:

> In most circumstances the introduction of safety legislation within a country has followed a major accident or incident. Regulation has been reactive whereas for modern biotechnology the system of regulation has been proactive. There are no documented cases of harm resulting directly from the use of recombinant techniques,

[92] See: www.haiweb.org/indexPharmageddon.html.

> whether in the research environment or for commercial applications. There are many who ask whether a proactive approach to biotechnology regulation is sensible, for it places in the public domain a concern that has been translated into a fear of the new technology, particularly in Europe. Would most of the innovations that have so fundamentally modified our way of life during the twentieth century have happened had a full risk evaluation been required?[93]

Any survey of the literature and of expert opinions on this matter encounters contradictions, apparently because it is as yet not possible to foresee what the principle health products emerging from this field will be. Regulatory experts consulted in the course of compiling this report have been hesitant to predict future developments, though they have contributed some useful hypotheses. It is therefore extremely difficult to suggest in which manner public policy on these issues should proceed in the coming years, because of uncertainties in the development and output of biotechnology over the coming years. It is even more difficult to predict the manner in which public policy actually will proceed in view of the various pressures to which policy makers are subjected. In this respect we use the word "policy" rather than "regulation" since it is broader and more meaningful. Policy indeed involves making and implementing laws and regulations, but it also involves education, allocation of resources, provision of information – and where appropriate – a degree of persuasion and attempts to attain consensus.

Where biotechnology and its effects on health are concerned, attainment of consensus may prove to be a distant goal. Insofar as the debate relates to artificially modified crops, for example, commercial pressures and public opinion have been in conflict for well over a decade. This is well illustrated by the debate on genetically modified (GM) foods. In North America, commercial pressures have largely won the day, and a very wide range of foods and other products are on sale incorporating GM or other biotechnologically inspired innovations. In Europe, by contrast, public concern has weighed more heavily. For other types of biotechnological innovation, the balance could be different. In medicine, biotechnology has already demonstrated its ability to treat successfully conditions that were hitherto not amenable to therapy; particularly where these are rare disorders with a poor prognosis, there will be a considerable willingness both among patients and regulators to accept them together with their possible risks. As in the drugs field, however, both public thinking and political priorities are likely to be swayed by individual events and accidents. It is not inconceivable that if any evidence were to emerge that a genetically modified microorganism, readily transmitted around the world, could possess serious pathological properties, public concern would become the dominant influence on policy even in North America and certainly elsewhere. Conversely, if a number of years of experience with genetically modified crops in China and North America were to deliver no evidence of harm, that particular type of innovation might be more readily accepted in Europe. The impossibility of looking very far ahead where biotechnology is concerned renders it vital to revise one's outlook at regular intervals. As OECD looks ahead to 2030, it should, while laying down certain principles, surely call for a constant reassessment of practical policy in this constantly evolving field.

[93] Kinderlerer J. (2007):.

8. Bibliography

Other relevant literature used in this report is cited in the form of references presented as footnotes throughout the text.

Abraham, J. and H. Lawton Smith, eds. (1993), *Regulation of the Pharmaceutical Industry*, Palgrave/Macmillan, Houndsmills, Hampshire.

Attaran, A. (2003), *Malaria Drug Treatment: Prescriptions for Curing Policy*, Paper presented to the UN Millennium Task Force, on Access to Medicines.

Angell, M. (2004), *The Truth About the Drug Companies,* Random House, New York.

Black, D. (1987), **TO BE ADDED**.

Business Insights (2007), Drug Development Opportunities In China: Regulation, Key Players and Initiatives for Domestic and International Markets, New York, 20 January.

Byrne, J., G. Conko, J. Entine, T. Gilland *et al.* (2006), Edited by Jon Entine, AEI Press, Washington.
Collier, J. (2002), "Regulating the Regulators", *Lancet, 360,* p. 2199.

Dukes, M.N.G. (1985), *The Effects of Drug Regulation,* MTP Press Ltd for World Health Organization, Regional Office for Europe, Copenhagen.

Dukes, M.N.G. (2002), "Accountability of the Pharmaceutical Industry", *Lancet, 360,* pp. 1682-1684.

Edwards, I.R., ed. (2005), Regulation of Vioxx: Success or Failure? (Summary of a discussion between experts), Uppsala Reports, April, pp. 11-13.

Finegold, D.L., C.M. Bensimon, A.S. Daar *et al.* (2005), *Bioindustry Ethics*, Elsevier/Academic Press, Amsterdam, Boston, Heidelberg etc.

Food Standards Agency (London) (2007), Safe Food and Healthy Eating for All (Website), GM and Novel Foods, Consulted 18 October 2007.

Foster, C. (2003), "What Are Ethics, and Can They Be Regulated?" in J. Abraham and H. Lawton Smith (eds.), *Regulation of the Pharmaceutical Industry*, Palgrave Macmillan, London.

Hu, M., K. Shulz, J. Scheu and D. Tschopp (2007), *The Innovation Gap in Pharmaceutical Drug Discovery & New Models for R&D Success*, Published by the Kellogg School of Management, Document HIMT 455.

Kinderlerer J. (2007): Regulation of Biotechnology: Needs and Burdens for Developing Countries. Unpublished paper.

Kling, J. (2006), "Merck Moves into Biotech", *Nature Biotechnology,* 24(7), *p.* 730.

McHughen, A. (2000), *Pandora's Picnic Basket: The Potential and Hazards of Genetically Modified Foods*, Oxford University Press.

Milne, C.-P., J. Tait, L. Cabanilla and J. Wegner (2007), *Evolution Along the Government-Governance Continuum: Impacts of Regulation on Medicines Innovation,* Manuscript in preparation, cited from report for OECD "Human Health Scenarios" by Tait *et al.*

Mittra, J. (2007), "Life Science Innovation and the Restructuring of the Pharmaceutical Industry: Merger, Acquisition and Strategic Alliance Behaviour of Large Firms", *Technology Analysis and Strategic Management, 19(3),* pp. 279-301.

National Centre for Biotechnology Education (University of Nottingham) (2006), GM Food Information. *This Was the Food That Was?,* Web publication.

National Institute for Health Care Management Research and Education Foundation (2002), *Changing Patterns of Pharmaceutical Innovation*, May.

OECD (2007a), *Definitions of Biotechnology for the Bioeconomy to 2030*, OECD, Paris.

OECD (2007b), *Human Health Biotechnologies to 2015,* OECD, Paris.

OECD (2007c), *Baseline Assumptions about Long Term Global Trends Shaping the Development of the Bioeconomy,* OECD Futures Project on the Bioeconomy to 2030: Designing a Policy Agenda, Paris.

Organization for European Economic Development (1969), *Gaps in Technology – Pharmaceuticals* (Rapporteur: M.N.G.Dukes), OECD, Paris.

Parisian, S. (2001), *FDA: Inside and Out*, Fast Horse Press, Front Royal, Va.

Paugh. J. and J.C. Lafrance, eds. (1997), *Meeting the Challenge: US Industry Faces the 21st Century. The US Biotechnology Industry,* US Department of Commerce, Office of Technology Policy, July.

Penn, R.G. (1979), "The State Control of Medicines: The First 3000 Years", *Bri. J. Clin. Pharmacol.,* 8, pp. 293-305.

Price Waterhouse Coopers, *Pharma 2020: The Vision*, available at pwc.com/pharma.

Smith, Jeffry M. (2003), *Seeds of Deception: Exposing Industry and Government Lies About the Safety of the Genetically Engineered Foods You're Eating*, Yes! Books.

Tait, J. and R. Williams (1999), "Policy Approaches to Research and Development: Foresight, Framework and Competitiveness", *Science and Public Policy*, 26(2), pp. 101-112.

Thomas, L.G. (1990), "Regulation and Firm Size: FDA Impacts on Innovation", *RAND Journal of Economics*, 21(4), pp. 497-517.

Tokar, B., ed. (2001), *Redesigning Life?* Zed Books.

United Nations (2005), *Access to Essential Medicines: Final Report from Task Force 5 of the United Nations Millennium Development Goals Project: Infectious Diseases and Access to Essential Medicines*, Working Group on Access to Medicines, UN Millennium Project, United Nations, New York.

Wield, D., J. Chataway and D. Kale (2007), "Frameworks for Pharmaceutical Innovation in Developing Countries: The Indian Case", *Technology Assessment and Strategic Management*, 19 (5).
Wigmore, J.H. (1914), "Introduction" in H.B. Hemenway, *Legal Principles of Public Health Administration*, cited by W.J. Curran and E.D. Shapiro (1970*), Law, Medicine and Forensic Science*, Little, Brown and Company, Boston and Toronto, at p. 669.

World Health Organization (2003), WHO Policy Perspectives on Medicines: No. 6, *How to Develop and Implement a National Drug Policy*, Geneva, January.