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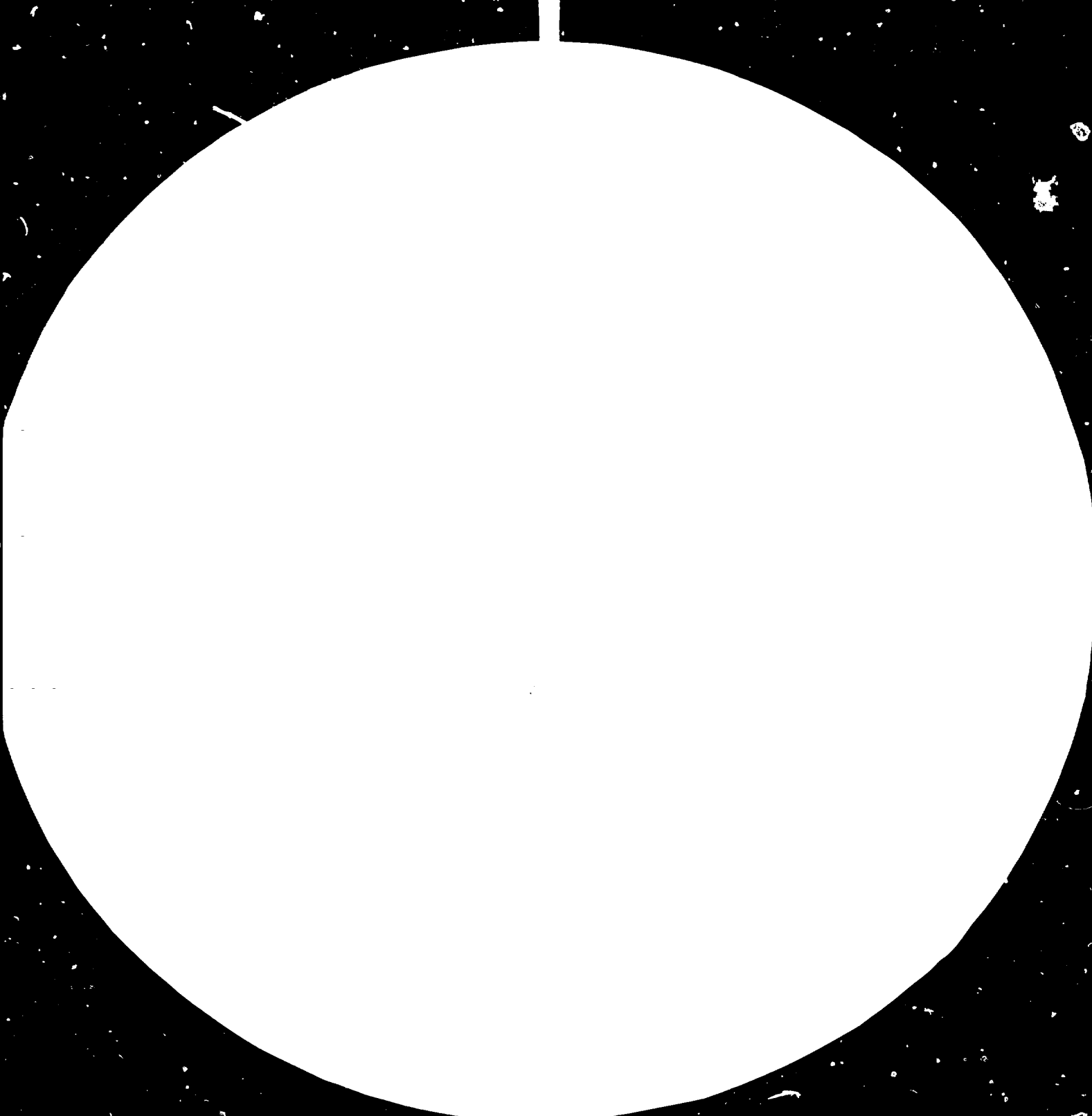

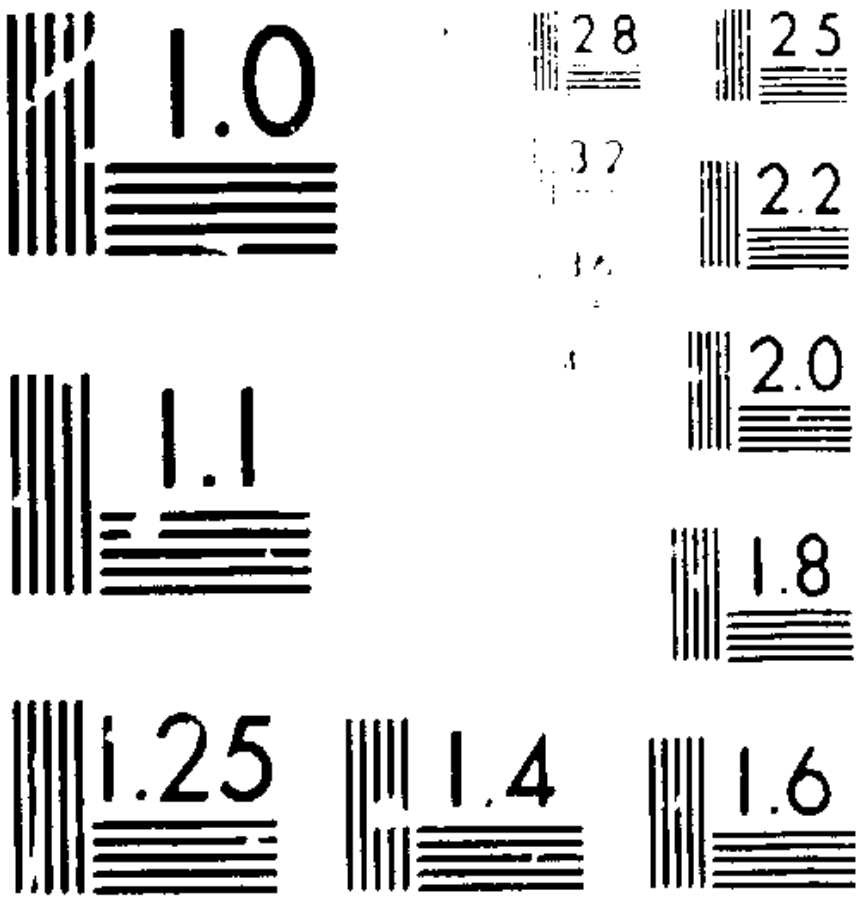
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COMMERCIALIZATION OF GENETIC ENGINEERING TECHNOLOGIES: SOME CONSIDERATIONS

Prepared by

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1. This paper discusses briefly, in an illustrative manner, some important considerations in the commercialization of genetic engineering technologies, viz preconditions and time horizons for commercialization; agents of commercialization; and patents. It concludes with remarks on options for developing countries.

Preconditions for Commercialization

2. There are broadly three preconditions for turning genetic engineering into a large industry:

a) Identification of a commercially useful biochemical product;

b) A fermentation technology to scale up to commercial production;

c) The engineering of efficient microbes for commercial production.

The rate of commercialization will be governed by these three conditions which are inter-related and can be met in any order.

3. As regards the end product, commercial potential varies with the product. While there are already several examples of new products created through genetic engineering and in some cases the microbe itself may be the final product, large market potential is at present perceived in regard to established biochemical products for which the genetically engineered products will be cheaper, and in cases, less energy intensive substitutes. Products in sectors such as food processing; chemical and pharmaceutical industries including fertilizers, pesticides and detergents; mineral processing; and recycling and waste treatment are likely to be involved. 1/. An expert report in the United Kingdom makes the following assessment 2/: "we envisage biotechnology - the application of biological organisms, systems or processes to manufacturing and service industries - as creating wholly novel industries, with low fossil energy demands, which will be of key importance to the world economy in

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1/ Products reported to be on the way to commercial production include human insulin, interferon, human growth hormone, some biological pesticides, and vaccines for foot and mouth disease and scour.

2/ "Biotechnology: Report of a Joint Working Party," Her Majesty's Stationery Office, (March 1980)

the next century. Over the next two decades, biotechnology will affect a wide range of activities such as food and animal feed production, provision of chemical feedstocks, alternative energy sources, waste recycling, pollution control, and medical and veterinary care. We are convinced that it will shortly be possible to use microbial and other cells to make a wide range of organic chemicals which either cannot at present be made economically on a large scale or, if they can be made, require extensive inputs of land, energy and capital plant for their production from feedstocks, such as oil, which will become more expensive."

4. As regards fermentation technology, fermentation processes are difficult to scale up and the economics have to be assessed carefully. In scaling up not only is contamination by wild microbes liable to occur but also a wide range of other problems can result in a noticeable drop in the efficiency of the microbes. Thus fermentation technology can be said to hold the key to commercialization. Adoption of such technology may not be so much of a problem financially in pharmaceutical and food processing industries which already use such technologies as in chemical industries where a switchover from high temperature and energy intensive processes may be involved.

5. As regards the engineering of efficient microbes, rapid progress is occurring at present. The question can, however, be asked why the initial thrust of commercial application of genetic engineering has been in the biomedical field. It is argued that it is because of the large data base provided by many years of basic research in a specialized area of microbiology and the general area of biochemical and biomedical sciences. Thus what might at first analysis appear to be a rapid exploitation of genetic engineering actually resulted from the accumulation of information generated over at least thirty years of intensive investigations. It is, therefore, argued that the extension of genetic engineering to other areas of commercialization such as agriculture will require longer development times to gain the critical basic knowledge not now available.

At the same time, given the rapid progress and the possibility of unexpected break throughs it would not be correct to consider commercialization in other industries as long term propositions [1]. (See the section on Time Horizons for Commercialization).

6. The preconditions stated above make it clear that successful commercialization is a transdisciplinary effort requiring a team of [2]:

a) competent and creative scientists trained in the academic community;

b) biochemical engineers for scale up and production;

c) a competent management, including patent attorneys, general counsellors, financial strategists, marketing specialists, etc;

d) quality control personnel;

e) the development of laboratory and animal facilities; and

f) pilot plant facilities.

In addition, much of the commercial application of genetic engineering being based on fermentation technology, the team will require chemical engineering inputs in the design of standard and specialized fermenters.

Time Horizons for Commercialization

7. Several assessments of the timetable for commercial production of various compounds and their market potential have been made by genetic engineering and market research companies. If one analyses the projections of the Office of Technology Assessment of the Congress of the United States, [3] they envisage a world market value of some 3.5 billion US dollars in five years, another 17.5 billion in ten years, and 3 billion more in fifteen years. These projections should be considered as under-estimates

1/ See UNIDO report on "Exchange of Views with Experts on Implications of Genetic Engineering for Developing Countries"(IS/259) p. 9

2/ ibid; p. 18

3/ See annex to UNIDO paper on "The Impact of Genetic Engineering on Industry (IS/ 269). For details see "Impacts of Applied Genetics: Microorganisms, Plants and Animals". Office of Technology Assessment U.S. (OTA-HR-132, April 1981) Appendix IB.

since the figures included in the projections for the important areas of aliphatics and aromatics are for the United States only and for all products existing rather than future market values are taken into account. Food processing industry is not covered either. In terms of industrial sectors, many pharmaceutical products are likely to be commercialized in the next five years, except vitamins and antibiotics which might take ten years. Commercialization of products in aliphatics and aromatics is expected to start substantially within five years but the full impact could be seen within a ten year period. Inorganics (ammonia, hydrogen) are expected to be commercialized within a fifteen year time frame. However, as already stated, in this dynamic field it would be difficult to forecast with full confidence the time horizons involved.

8. A Delphi Study [1/] conducted through a diverse panel of twenty-two experts revealed a rather high degree of agreement on the expected timing of the events for industrial break throughs as distinct from break throughs in other fields. Over 75% of the panelists felt that technologies for waste water treatment and development of petrochemical substitutes (e.g. pesticides and oil/lubricant substitutes) would be fully marketable by the years 1990-2 at the 50% probability level. Taking the 90% probability level moved the dates only slightly. The panelists mentioned two major obstacles to implementing the industrial proposals: the risks of contaminating workers with hazardous rDNA materials and the increasing dangers of release of organisms as the scale up production increases.

9. Irrespective of different projections,[2/] the perceptions of entrepreneurs and investors in industrialized countries have been such as to result in a state of hectic corporate activities.[3/]

Agents of Commercialization

10. In the commercialization of genetic engineering a closer relationship

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1/ Recombinant DNA breakthroughs in Agriculture, Industry and Medicine: A Delphi Study by Shelby Stewman, David Lincoln et al in Futures, April 1981, pp 128-140

2/ Several other projections have been reported by Genex, Chicago Group / Policy Research Corp., International Resource Development and Byers. A French report by SEMA has also been reported.

3/ More than a year ago. US investment was estimated at $500 million and worldwide at $1 billion expected to grow 5-fold by 1985 (Chemical Week, June 25, 1980 p.37)

between industry on the one hand and the university on the other is evident than in most other industries. The distinction between basic and applied research wears thin in this field. Several current trends in this field may be listed as follows: 1/

a) Several universities have been directly involved. For example, Stanford and California universities license basic genetic engineering techniques. 2/ Harvard thought of forming a company but finally decided against it. In France the scientists of one university (Universite de Technologie de Compiegne) have formed a company.

b) A large number of small ventures, estimated over 80 some time ago, have been formed with a large number of well-qualified scientists and technicians as the core staff 3/.

1/ This is based on a review of diverse journals and reports.

2/ Recently Stanford University announced the price of licence for the basic genetic engineering patent (US 4,237,224) (which covers techniques essential to all genetic engineering) it shares with the University of California.

All licensees will pay $10,000 each year in fees. Their royalties will be determined by the type of genetic engineering business the company wants to pursue. There are four basic categories:

a) End products - On products sold ready for use, the royalties will vary from 1/2% to 1% of yearly sales. Companies selling less than $5 million each year will pay the whole 1%; those selling more will pay less.

b) Intermediate products - Companies selling genetically engineered products that another firm might use for its genetic engineering work will pay 10% of yearly sales in royalties.

c) Bulk products - Companies selling gentically engineered products that must be upgraded for sale will pay from 1% to 3% of sales in royalties.

d) Process improvement - Companies using genetic engineering to make cost savings in a production process must pay as royalties 10% of the savings they realize.
(Economist, 8-14 August 1981, p. 67)

3/ Over 200 firms are reported to be involved in commercial gene splicing efforts in the United States. Some well known genetic engineering companies include Cetus, Genentech, Genex, Biogen, etc.

c) The interest of pharmaceutical, petroleum and chemical trans-nationals has been considerable..[1/] They have not only acquired shares in the genetic engineering companies but some of them have made substantial research grants to universities. The trans-nationals have the marketing and financial muscle which many of the new venture companies lack. As at present, the relation between the two types of companies appears to be one of mutual dependence.[2/]

d) Industrial enterprises are trying to join together. In the case of Japan a biotechnology research association has been formed with fourteen participating companies .[3/] In the United States an industrial biotechnology association of genetic engineering companies has been formed, not for research, but for government relations and protecting the common interest of the members.

e) A new type of venture with government participation is emerging. In the United Kingdom Celltech has been formed this way with participation by the National Enterprise Board. In the province of Ontario, Canada, a venture has been formed with the participation of the Provincial Government of Ontario.

f) Several companies manufacturing equipment for the new industry have been initiated, including automatic gene synthesizers (e.g. Biologicals of Toronto, Biochemicals of Arizona, USA) .

1/ To name only a few, Bristol-Myers, Eli Lilly, Hoechst, Hoffman-La Roche, Due Pont, Monsanto, Dow Chemicals, Standard Oil, Shell Oil.

2/ "In ten years,when today's discoveries are coming to commercial fruition, the small companies may be a thing of the past, with their scientists just a small part of the multinationals." (Comment in New Scientist, 10 November 1980, p. 348)

3/ The association will develop know-how on recombinant DNA applications bioreactors and the mass culture of cells. Several firms noted for fermentation technology are involved. (Chemical Week 10 Aug 1981 p.38) This combined with the progress already made in Japan in fermentation should give it an advantage in the commercialization of genetically engineered technologies.

11. While it is too early to generalize on the trends in technology transfer in genetic engineering, a few developments may be noted in passing. A genetic engineering company has formed subsidiaries both within and outside its country of origin. Genetic engineering companies have entered into licensing arrangements with pharmaceutical companies for manufacture of products such as insulin and human growth hormone. A measure of inter-country licensing has also been noted. Stanford and California universities have also obtained the rights to license certain basic genetic engineering techniques and conditions for such licensing have been announced,

12. Participation in the equity of genetic engineering companies by large transnationals in the pharmaceutical, chemical or energy fields will provide another vehicle for technology transfer from the former to the latter, though it is reported in some cases that the licences would be on a non-exclusive basis. The movement of scientists from one company to another would be another vehicle of technology transfer though the extent of such movement has not been much reported as in the case of micro electronics.

13. There is some evidence to suggest that when it comes to commercial production it may be the trans-nationals that may be the final agents of production. In that sense technology transfer to developing countries for several pharmaceutical products may be through the traditional route of pharmaceutical trans-nationals giving rise to well known issues in transfer of technology. When it comes to production, the same trend is likely to repeat itself in the chemical industry as well. 1/ Here the decision of whether or not to commercialize and later license genetically engineered chemical technologies will rest with the chemical trans-national which will look to its global market, its current investments in established processes and other considerations, rather than the developing country situation. The position with regard to petro-chemicals could be expected to be particularly difficult since technology and production routes could be through petroleum, coal based methanol or biomass.

14. Another consequence of commercialization through trans-nationals will be that the scale of commercialization will be large and the investments correspondingly high. 2/

1/ It is estimated that genetic engineering will have an impact on some 25 to 40% of the chemical industry.

2/ There is as yet not much information on the scale of investments required. A new plant in U.K. for production of insulin through genetic engineering methods (Eli Lilly) is said to involve an investment of $40 million.

Patents.

15. The existence of proprietary rights in either the developed or developing countries may have an effect, one way or the other on the efficacy of any genetic engineering technology transfer.[1/] In this regard, two types of proprietary rights are primarily involved: viz trade secrets; and patents . Researchers in most private industries are restrained in the discussion of their work by corporate policies to keep developments in an area secret. The technology is often uniquely susceptible of exploitation as a trade secret, particularly where the commercially valuable commodity is a metabolic product of a modified organism (i.e. where the inventions cannot be "reverse engineered" from the product sold). While trade secrets are almost uniformly protected throughout the developed countries, encouragement of maintenance of trade secrets has the dangerous effect of suppressing dissemination of information.

16. The intellectual property laws of the developed countries have kept pace with developments in this area and generally now provide for patents to be issued on many genetic engineering inventions, including modified organisms themselves. The position is briefly as follows·

17. The Supreme Court of Justice in the United States reversed, by a narrow margin of 5 to 4, earlier decisions by the Patent and Trademark Office of the United States and accepted patentability of "human made micro-organism."

1/ This section is based on the UNIDO report on "Exchange of Views with Experts on Implications of Genetic Engineering for Developing Countries" (IS/259).

18. In the Federal Republic of Germany both the micro-organism invention, that is, the micro-organisms as such as well as the process of using the micro-organism can be patented, however, it is necessary that the micro-organism be deposited at the culture collection at the time of filing the application. Furthermore, the product claims for the micro-organism per se are also patentable; the pre-condition for granting a patent for such micro-organism per se is that the inventor should disclose a repeatable method for the production.

19. According to the European Patent Convention an invention can be granted a patent concerning the micro-biology process where a product of the invention covers the use of micro-organism which is not available to the public. As in German Law such micro-organisms are to be deposited and should be in certain cases reproducible.

20. According to the Japanese Patent Law the micro-organism per se can be patentable provided that they can be reproduced. There is a special description regarding specifications which should be filed for the invention of the micro-organism.

21. According to the United Kingdom Patent Law, patents claiming micro-organisms per se have been granted for many years.

22. The patent laws of the developed countries are siad to be founded on two basic tenets, namely:

(a) That full disclosure of the invention to the public with attendant technological advancement is the price for limited private exclusivity; and

(b) that exclusivity is the best inspiration for rapid commercialiation of new technology.

Whether these tenets are correct in developed countries, and whether they are applicable to developing countries at all, is the subject of some debate.

23. The current debates regarding patenting of micro-organisms in developed countries relate to the degree of disclosure to be required in exchange for exclusive rights and the scope of rights to be granted.

24. The disclosure of novel micro-organisms has been facilitated by the Budapest Treaty on the Internaitonal Recognition of the Deposit of Micro-organisms for the Purpose of Patent Procedure (April 28, 1977). This treaty legitimises existing national practice by providing for

international recognition of a deposit of a sample of a micro-organism in an acceptable depository, to be made availabel to the public upon the issuance of a patent, as an aid in fully disclosing a micro-organism referred to in a patent application. Debate persists, however, as to whether detailed taxonomic and other written descriptive material must be included in the patent application in addition to the deposit. Indeed, whether the deposit should be required at all where the micro-organism involved is either readily available to the public from other sources or can be predictably manufactured from such available organisms by specifically described recombinant DNA techniques is also being debated. Also in question is whether the starting organism or the genetically modified micro-organism or both must be deposited.

25. The second major area of debate seems to be the scope of patent claims to be allowed in a micro-organism patent. Should disclosure of one or a few strains entitle the applicatn to claim the species? Should disclosure of one or a few species entitle the applicant to claim the genus? How predictable must the micro-organism modifying process be to support broad claims?

26. Regarding legal condiderations of technology transfer and ownership generally, some questions have been raised regarding the intellectual property law climate which should be provided in a developing country seeking genetic engineering expertise. It has been suggested that elimination of trade secret and patent protection in the developing country might "free-up" the technology. However, it has also been contended that, because much technology is privately owned, technology transfer to developing countries might be more likely where proprietary rights generally similar to those in developed countries exist.

Options for Developing Countries

27. Developing countries have an option to acquire existing commercial technologies and establish production. The establishment of production will itself stimulate a measure of capability in the application of the new technologies, particularly if R and D personnel are associated in the import and application of the technology. In the process, adaptations might be made to suit the country's conditions but may be of more general application as well.

28. However, the basic technological capability will be developed in the host country enterprise only if it can genetically engineer micro-organisms by itself. Otherwise, it is at best only the fermentation technology that the enterprise will absorb. Depending on the host country capabilities, the technology transfer could be through arrangements with:

(a) universities like Standford and California for license of basic genetic engineering techniques (if host country patent laws so require);

(b) licenses from or joint ventures with genetic engineering companies;

(c) licenses from or joint ventures with well establishes companies in drugs and pharmaceuticals, chemicals or petroleum, as the case may be.

29. It should be noted that irrespective of the nature and extent of technology transfer, the building up of technological capabilities to negotiate and absorb the transfer is imperative. As the White Paper on biotechnology of the Government of the United Kingdom says " at this stage, the need is to participate fully enough in fundamental and applied scientific research to expand all the possibilities and to create a climate in which selective development can be undertaken by those, best able to perceive needs and assess the possibilities and risks." 1/ The education and training of qualified personnel would require particular attention in this respect.

30. There is also a need for developing countries to participate, on a more equitable basis, at the global level in the further development and commercialization of technology advances in this important field. This would call for an imaginative approace, extending beyong the traditional modes of technology transfer. Other possible avenues to be explored would include:

1/ Her Majesty's Stationary Office, London (March 1981) pp. 11

a) co-operative efforts through an international facility and transfer from such a facility; and

b) transfer from the public domain in the developed countries.

In most of the developed countries basic research is in the public domain and mechanisms should be created by which genetic engineering technology could be transferred from the public domain to developing countries.

31. The possibilities mentioned above do not, however, answer the point that the technologies and products developed will be those that are suitable to developed country conditions and for which market potential exists. The suitability of fermentation technologies in developing country conditions may also have to be assessed. No doubt, R and D relating to developing country problems have been reported such as malaria, foot and mouth disease and chagas disease. However, the vast amount of work that needs to be done for developing country problems has to be done by developing countries themselves. Essential to such work would be a survey and assessment of the bio resources that developing countries possess, which is considered to be a "treasure chest." 1/ Work on small-scale fermentation will also be necessary.

32. To ensure commercial production, enterprise in developing countries in fields such as drugs and pharmaceuticals, chemicals and food processing will have to get involved in assessing the potential of genetic engineering techniques and developing basic capabilities to handle them. This may call for special R and D efforts in enterprises themselves or their linkages with academic institutions. Governments of developing countries may have to encourage such research efforts on the part of enterprises and also consider possible new enterprises involving government agencies, universities and industry. The R and D should include not only genetic engineering but also fermentation technologies.

33. Governments of developing countries may have to take a decision whether micro-organisms are patentable. If they are considered patentable, consideration could also be given to the introduction of certain new elements

1/ For the potential for developing countries, see C.G. Heden "The potential impact of Microbiology on Developing Countries" (UNIDO IS/261).

in the national patent laws in developing countries, which might facilitate faster access to proprietary technologies. This might include shorter duration of patent life, full disclosure provisions extending to commercial utilization information, requiring domestic exploitation of the patent by the patent holders, foreign investment regulations, etc.

34. Governments of developing countries may also have to pay attention to the question of developing safety guidelines for research and production, keeping in view considerations of human health and environment. 1/

35. The foregoing are only some of the considerations that could be envisaged. Further analysis by developing countries and actual experience may bring up other issues and possibilities.

1/ For a detailed discussion in the United States context see Chapter 11 of "Impacts of Applied Genetics", op.cit.