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The commercialization of biotechnology: the shifting frontier

by

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1. Introduction

During the 1980s, as advanced biotechnology moved out of its infancy, science push optimism gave way to a more realistic appraisal of what could be expected from the technology. Not that anyone questioned biotechnology's potential for becoming a driving economic force in the 21st century, but it became progressively evident that putting the new scientific knowledge to industrial use was a considerably more formidable task than had initially been surmised; the path from laboratory to marketplace was strewn with obstacles of all sorts.

As this awareness has increased, so have attempts by both government and industry of the advanced economies to tackle the obstacles. These efforts, which are all borne of the same basic interest, i.e. to enhance country and/or company competitiveness in commercial biotechnology, are being undertaken on many fronts at once. For instance, several countries are applying specific measures to overcome specific barriers to innovation while simultaneously confronting larger questions of public policy and industry structure and organization as these facilitate or hinder progress in biotechnology (and other knowledge intensive industries). Innovative steps are also being taken by the biotech industry itself. Thus, in a recent precompetitive move, the major industrial biotechnology associations of the U.S., Japan, the EC and Canada have undertaken to develop a common approach in policy areas deemed critical to the industry's overall success; significantly, the first such area to have been targeted is biosafety regulation[1].

In fact, country differences in areas such as industrial policy and corporate culture notwithstanding, a salient feature of the increasingly international environment in which biotechnology is evolving is the growing *de facto* consensus among national governments and industries as to the requirements for and obstacles to a growth-oriented and globally competitive biotechnology industry. This is spelled out in recent policy statements of the various governments and in private sector reports. It is also evidenced by actual steps being taken by industry. For instance, while the United States has begun to work at strengthening its downstream scaleup skills and capabilities, Japan has been moving upstream into basic research.

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* Many of the points developed in this paper have received a more thorough treatment in: F.Seroovich and M.Leopold, 1991.

The fact that countries and companies are increasingly aggressive in attempting to identify and overcome barriers to competitive market entry is a clear indication of the dynamism of the industry. But it is also an indication of the importance of those barriers. The translation of scientific discoveries into useful and competitive products is simply not a small matter. In fact, since the breakthroughs of the early 1970s' that laid the foundations for the new biotechnology, relatively few products have actually been commercially marketed, while literally hundreds are being held up at various phases of the innovative chain. It would thus appear that factors that are slowing up product development, approval and commercialization are presently more than offsetting factors that are propelling the process forward.

In the following pages we identify some of the main impediments to the timely introduction and diffusion of the products of biotechnology as well as various measures that are being taken to counter them. Developing countries seeking competitive entry into biotechnology have everything to gain by drawir , selectively on these experiences.

Obstacles to commercialization in biotechnology are quite variable in that they often differ in importance according to country, application sector and user-industry, company size, learning-curve and other time-related considerations, changes in the macro-economic climate. Furthermore, factors that hamper innovation under certain conditions may actually accelerate it under others. Since the limits of the present paper make it impossible to take full account of these and other variables and the complex interplay among variables, our approach should be considered indicative.

We have drawn heavily on the U.S. experience, which is the most important to date, and for which there is the greatest amount of readily available information. Furthermore most examples relate to therapeutic and agricultural applications of biotechnology, where entry barriers are considerably higher than in the diagnostic and supplier sectors of the industry. For reasons related, among others, to the state of basic knowledge, competitive potential, entrenched corporate interests, policy priorities, other application sectors such as chemical production and bioremediation presently lag far behind and will not be dealt with

Although most of the bottlenecks, scale factors and entry barriers discussed here should decrease in importance as commercial biotechnology moves up the learning curve, considerable time will elapse before timely market introduction becomes the rule rather than the exception

2. Scientific, technological and engineering bottlenecks

Ultimately, if the products and processes of biotechnology are to be commercially successful, they must hold a competitive advantage over existing products and process or, should they be entirely new, they must correspond to market demand/social need. Even in the case of engineered drugs like human insulin, human growth hormone, alpha interferon, t-PA and erythropoietin, high relative prices and technical difficulties are impacting market size.

Some of the factors interfering with competitive market entry have to do with as yet unresolved scientific, technological and engineering problems. A sample of such bottlenecks serves to illustrate this point.

Despite unprecedented scientific and technological advances over the past decade, major bottlenecks in basic and applied knowledge continue to affect research aimed at the development of human therapeutics. Knowledge gaps in the field of protein drugs concern the structure, function and engineering of proteins, the effect of metabolism on gene expression, and drug delivery methods. (F.C.Sercovich and M.Leopold,1991; OTA,1988)

One of the major challenges to the development of protein and peptide drugs has been that of finding appropriate delivery systems. The large and delicate molecules of drugs such as human and animal growth hormones, human insulin, and interferon cannot be delivered orally, because they are degraded by stomach enzymes. With injection as the only method of administration, market size is limited. In the cutting-edge field of antisense therapeutics, delivery is turning out to be an even more formidable obstacle: in addition to resisting enzymic degradation at target sites, effective, yet not toxic, doses of compounds will have to accomplish the difficult task of penetrating cells. It is thus possible that commercial application of the antisense approach will be put on hold until the advent of drugs that either cause genes to produce antisense substances within the cell or use lipid coatings capable of fusing with the cell (M.Ratner, 1991).

Equally important unresoved questions in the field of protein drugs involve the structure, function and engineering of proteins. Since protein engineering - a critical step at the biotechnology frontier - requires understanding the protein's function, which in turn depends upon its shape, considerable and costly efforts have been undertaken to unravel protein structure (including attempts at protein crystallization in space) (F.C.Sercovich and M.Leopold,1991). In this context, significant interest was aroused in April 1991, when researchers at the rational drug design company Agouron published the crystal structure of an

enzyme the HIV virus needs in order to replicate (D.A. Matthews et al., 1991). But other scientists were quick to question the importance of the discovery. In particular, it was noted that because the crystal structure described is that of an *inactive* protein, its usefulness in designing a drug to inhibit the virus remains to be proven. This and other uncertainties linked to the rational drug design process - which includes protein purification and crystallization, X-ray crystallography and computer modeling - are slowing innovation in protein engineering. (M.Ratner [b], 1991; J.O'C.Hamilton *et al*, 1991)

Curiously, these caveats do not seem to dampen investors' spirits. In fact, on the day following the publication of the enzyme structure, Agouron's stock shot up a spectacular 65% (J.O'C.Hamilton, 1991). In the same vein, commenting on the above-mentioned bottlenecks linked to antisense drug-delivery, one biotechnology financial analyst observed: "[t]here are loads of unresolved technical questions that [investors] don't seem to care about" (A. Berler in M.Ratner, 1991).

Important deficiencies in the stock of basic scientific knowledge have been recognized as seriously delaying developments in agricultural biotechnology. An insufficient understanding of key traits in plants has hampered the use of genetic engineering to produce certain types of transgenic plants, particularly when this involves multiple gene transplants. Although major efforts to overcome these obstacles are in the works - including, in the U.S., a ten year research project aimed at mapping the plant genome and a proposed reallocation of government basic research funds from medicine to agriculture and other areas - it will be well into the next century before agricultural-biotechnology can be expected to fully reap the benefits of these efforts.

Furthermore, advances in agricultural biotechnology will also depend upon progress in related areas. Thus, for instance, plants programmed to express insect-resistance, as well as biopesticides themselves, face a potential problem that has long plagued the chemical pesticide industry, i.e. the emergence of insensitive strains of pests (B.Dixon,1991). Failure to understand and master insect resistance to biocontrol agents can wipe out a potential competitive advantage of these agents.

3. Threshold factors

i. Research &Development

As mentioned above, barriers to commercialization are largely user-industry specific. In the R&D-intensive pharmaceutical industry, which is heavily involved in biotechnology, both soaring R&D costs and declining productivity have been affecting innovation rates. During the 1980s, R&D expenditures by the world's main drug companies increased fourfold, while applications to the U.S. Food and Drug Administration (FDA) to market new drugs dropped some 60%, and the actual introduction of new products has been falling since 1960. (M. Waldholz, 1991; J.O'C. Hamilton et al., 1991).[2]

In the case of dedicated biopharmaceutical companies, most of which are still in a precommercial phase, an average of 63 percent of product sales is spent on R&D, compared with 16 percent for traditional pharmaceutical companies (Burrill, G.S., 1989). Thus the relative burden of R&D costs is even greater.

These threshold factors, among others, are causing major industrial restructuring, including mergers, acquisitions and, prominently in the biopharmaceutical sector, strategic alliances (F.C.Sercovich and M.Leopold, 1991). Since 1988 no less than 15 major drug firms have consolidated, and the search for opportunities is becoming increasingly aggressive as companies seek to strengthen their R&D capabilities and underwrite the growing costs of doing so (M.Waldholz,1991). Meanwhile, dedicated biotech companies, which remain the driving force in the innovative process (and thus offer the possibility of partially offsetting declining productivity), continue to be the target of takeovers, with more than 30 U.S. startups being acquired between mid-1989 and mid-1990 (G.S.Burrill and K.B.Lee, Jr., 1990).[3]

Strategic alliances, which usually bring together a dedicated biotech firm and a large established corporation, are also an important means of overcoming R&D-related obstacles, insofar as they provide the smaller partner with financial resources and the larger partner with human or technological assets or with products[4]. In the U.S., such alliances presently represent the second most important source of capital for startups, after the public markets.

Another strategic move by industry to overcome R&D cost thresholds is in the area of pricing. The premium prices charged for new drugs in the U.S.[5] are explained by industry as necessary in order to generate the profits that finance major research[6]. In the case of biopharmaceuticals,

whether they be produced by established corporations or startups, pricing policy is particularly draconian; given the uncertain climate in which products are introduced, companies seek to recoup sunk R&D investments as quickly as possible (F.C.Sercovich and M.Leopold, 1991) . A case where the speed of investment recovery has been of the essence is that of Genentech's recombinant blood clot dissolver t-PA; priced at $2,200 per dose, the drug recently took a serious blow when it was shown to be no more effective than streptokinase, a synthetic heart attack drug marketed at $186 a dose.

These high relative prices have been facilitated by the so-called Orphan Drug Act of 1983, which grants seven year monopoly conditions to companies developing new drugs for diseases affecting fewer than 200,000 people. Companies have, furthermore, drawn scope-economies from the Act through a loophole in FDA regulatory policy that allows doctors to prescribe a drug for off-label uses; by targeting the narrowest indications for regulatory approval, companies thus qualify for orphan status designation, while at the same time positioning themselves to cash in on the benefits of broader off-label indications (for which, to boot, costly clinical trials have been avoided). Human growth hormone, for instance, was originally approved for treating growth hormone deficiency, but has obtained orphan status for 11 indications involving four drug companies, and commands a large market for the treatment of burns and aging. Orphan status has allowed some $200 million in annual sales of both hGH and Epo (J.G. Thoene, 1991).

A still embryonic approach to actually bringing down the costs of R&D and to increasing productivity involves targeting the techniques of drug research itself. As mentioned, the time-consuming and inefficient random screening of chemicals used in conventional drug research, has a lot to do with increasing costs and declining productivity. A small number of new startups are in the process of "rationalizing" drug development by integrating the research techniques of genetic engineering with the chemical synthesis process; biotechnology is used as a set of research tools to create the smaller and less expensive to produce molecules of chemical synthesis.[7]

II. Production

Production-related threshold factors have not received as much attention as those linked to R&D. Low production volumes, high returns, as well as the science driven nature of biotechnology, all contribute to explain a situation whereby, until recently, efficient production processes were not a priority issue.

This is not to say that companies were unaware of the complexities involved in bioprocessing scale-up; clinical trials in pharmaceuticals already require scale-up capabilities, and companies seeking to be first to market in competitive situations have had to confront manufacturing-related technical and engineering problems early on (F.C Sercovich and M.Leopold). In fact, in the case of dedicated biotech firms, accessing production skills and capabilities has been an increasingly important reason for strategic alliances. But generally speaking, the efficiency of scale-up *per se* has not been given due consideration.

This is beginning to change; with competition and production volumes on the rise and profit margins bound to fall, scale-up cost-cutting is becoming increasingly critical to success in the marketplace. This is particularly so in the area of downstream processing (purification and protein recovery), which, in the case of biopharmaceuticals, represents upward of 50% of total production costs and as much as five times the cost of purifying traditional drugs (B.J. Spalding, 1991).

This bottleneck has given rise to innovations in downstream-processing technologies, where new approaches to cost reduction include perfusion chrometography, membrane affinity separations, protein refolding improvement and the engineering of recombinant proteins to include properties that improve purification.

More efficient technologies are a necessary but insufficient condition for downstream cost-reductions. For one thing, companies must be prepared to adopt the technologies, which, in the U.S. anyway, is not necessarily as easy as it appears. Because present analytical techniques cannot fully define recombinant proteins, the U.S. Food and Drug Administration (FDA) takes into account production processes when characterizing the proteins; this means that a change in process requires a new product license, which in turn increases lead times and costs.

Improvements in upstream processes are also still called for. Of note is the fact that, contrary to early expectations, bioreactors have not succeeded in replacing fermentors, despite the technology's greatly superior productivity on non-commercial scales. Scaling up has proven to be a major obstacle, as has the cell line specificity of the reactors. Other problems are related to the costs of building bioreactor plants as opposed to converting fermentors, and to the fact that companies racing to bring products to market are reluctant to use production techniques less familiar to federal regulators. This situation may change in the 1990s, as bioreactors are being used in the production of many pharmaceuticals presently in clinical trial, and improved bioreactors are coming to market, meanwhile a potential competitive advantage (related not only

to productivity levels but to operating and purification costs) is being lost. (B.J.Spalding [b], 1991)

The overall importance of scale-up as a barrier to commercial entry is corroborated by the fact that governments of the leading economies have manifest an interest in supporting industry efforts in this area. In the U.S. a recent expression of this interest is found in the 1991 Report on National Biotechnology Policy, which states that "[r]esearch focused on generic principles and procedures common to scale-up processes could generate large spillover benefits that could not be captured by any one firm and hence would be an appropriate area for Federal support" (President's Council on Competitiveness). Japan addressed scale-up problems early on.

Agricultural biotechnology presents its own set of production-related threshold barriers, which tend to be linked to agronomical rather than engineering problems. Although, as in pharmaceuticals, scale-up capabilities are required early on (i.e. for small-scale field trials), the type of difficulties encountered -- not only in seed scale-up but in all phases of the growth cycle -- relate to issues such as reproducing in the field results that have been obtained in growth chamber conditions, dealing with the seasonality factor and so forth. As in pharmaceuticals, maximizing yields, assuring a high degree of purity and reducing waste stream are major preoccupations, but most of these problems are confronted upstream, with process biologists working in the lab to design appropriate traits into host vectors.

iii. Market creation

Given the science-push nature of biotechnology, market demand, indeed social "need", sometimes has to be created more or less *ex nihilis* A case in point is that of Genentech's recombinant human growth hormone, Protropin, which was developed essentially because researchers discovered how to produce it. The natural U.S. target population of the drug, pituitary dwarfs, of whom there were only some 20,000 when the drug was approved (1985), would not have allowed the company to rapidly recoup its R&D expenses, even at an annual treatment cost of some $15,000 and under quasi-monopoly conditions afforded by the Orphan Drug Act. Genentech moved to solve this problem by making the drug available for children who, unlike pituitary dwarfs, are not hGH deficient but are below the third percentile in height.

This strategy was possible thanks to a number of ingenious marketing moves made by Genentech[8], and to the above-mentioned regulatory loophole, whereby doctors were not confined to prescribing Protropin for dwarfism By creating the perception that normal shortness is a

disease[8], Genentech has tapped into a potentially major market of 90,000 children born in the U.S. annually who will fall under the third percentile for height, and rapid sales growth has helped the company not only to recover R&D expenses, but to offset a stagnating market for t-PA, the cost-effectiveness of which, we have seen, has been seriously challenged.[10] (B. Werth, 1991).

Not all biotechnology companies have been able to create and service their own markets. In fact even when demand exists, accessing markets is a compelling reason for most dedicated biotech firms to either license their technology to or market through large established corporations with appropriate sales forces and far-reaching distribution channels (Genentech itself had to enlist the help of Eli Lilly to market its hGH overseas).

4. Regulation

It has been said and repeated over the years that biosafety regulation is one of the most important obstacles to the timely market introduction of the products of biotechnology. Any doubts about the truth of this observation should be dispelled by measures recently taken at both industry and government levels. As mentioned earlier, biosafety regulation has been targeted as the first area for precompetitive collaboration among the major industrial biotechnology associations of the U.S., Japan, the EC and Canada, the objective being to put pressure on the various national governments to harmonize regulatory principles, policies and practices. This attempt to reduce the effects of regulatory externalities on an increasingly global biotechnology industry concurs with the fact that companies regularly evoke experience with foreign regulatory systems as a reason for seeking alliances with foreign partners.

Also underscoring the importance of regulatory barriers is the fact that earlier this year both the U.S. and the E.C. came out with policy statements that focus largely on the effects of regulation on competitiveness (The President's Council on Competitiveness, February 1991; The European Commission, April 1991). Although in both cases a streamlining of the regulatory framework is sought, the respective approaches are markedly different, with the U.S. administration pushing towards greater laissez-faire -- a position not shared by those concerned with market failures --, while the EC puts the accent on standardization, by creating a Community-wide body of regulatory legislation that supplants national laws and regulations (and the effect of which is to relax rules in countries like Germany and Denmark, to tighten them in others, and to create a framework for oversight where little or none exists -- Italy, Spain, Portugal, Greece).

But neither government nor industry can will away the long lead times, costs and uncertainties linked to biosafety regulation (although certain policy measures could help to alleviate the situation). These entry barriers stem from to a complex interplay of factors, including bottlenecks related to risk assessment, uncertainties and overlaps as to regulatory jurisdiction, debates over product versus process based rules, a lack of qualified regulators and adequate infrastructure and, in the case of certain bio-applications, pressures from public interest groups. Most of these problems concern the U.S. and/or EC member states, while in Japan, where regulatory directives are much less detailed, much is left to discretionary decision-making and informal mechanisms.

i. Risk assessment. In the early years of the new biotechnology, there was concern among scientists and public interest groups about the accidental dissemination of genetically engineered microorganism (GEMs) designed for application in the contained environment of laboratories and industrial fermentation processes. The concerns subsided over time, as strict standards for physical and biological containment were adopted; furthermore, successive risk assessment experiments led to the conclusion that the rDNA techniques were not inherently dangerous and that most GEMs designated for large-scale industrial applications were of low risk. These conclusions in turn made it possible to apply traditional criteria for assessing biotherapeutics: safety, quality, efficacy.

As biotechnology moved into non-medical applications such as agriculture, bioremediation and leaching, different kinds of questions were raised: in these cases, the engineered organism or microorganism was not a means of production to be used within the confines of laboratories and bioreactors, but rather an end product designed to be applied in the environment. Thus misgivings shifted from potential risks linked to accidental discharge to health and safety risks associated with intentional environmental release.

At this point in time, environmental release remains a sensitive and widely debated issue, particularly between molecular biologists and ecologists. According to a National Academy of Sciences report (NAS, 1987), intergeneric organisms do not present unique hazards and most engineered organisms will not be as fit as their parent organisms. A contrasting view identifies the following ecology-related information gaps with regard to the release of GEMs : detection and monitoring; horizontal transfer of the genetic information of the GEMs; fate of the GEMs after release into the environment, e.g. survival and dispersion; effects of GEMs on the environment (Colwell *et al.*, 1988). One thing upon which scientists seem to agree is that GEMs present

greater potential risks than other transgenic organisms, such as plants and animals.

ii. Regulatory policies and politics. Making matters more difficult is the fact that biosafety regulation is not a purely technical process, founded in science and risk assessment. Regulating biotechnology is also a complex political process, aimed at fostering, or at least not undermining, economic objectives. In fact, the fundamental challenge posed to policymakers is precisely that of establishing a regulatory regime that strikes an acceptable balance between safeguarding the public and the environment, on the one hand, and, on the other, avoiding unnecessary impediments to the innovative process.

To date there is considerable disagreement among governments, within governments, and between government and industry as to the terms of that balance, the definition of which, moreover, appears to be shifting over time, as biotechnology becomes an increasingly high stakes international game. In any event, it can be safely said that, to some extent, all biosafety policies and the political processes in which they are enmeshed, are slowing up market entry.

In the U.S., the entire question of regulating commercial biotechnology coincided with the Reagan Administration's move to deregulate the economy, and as early as 1981, an executive Task Force set forth principles aimed at alleviating regulatory burdens on the private sector. This position was a determining force in shaping the so-called "Coordinated Framework for Regulation of Biotechnology", a series of proposed policy guidelines issued in 1986 and the essence of which was to affirm the principle of product-based (as opposed to process-based) oversight. Scientific considerations notwithstanding, assessing bioproducts on their inherent characteristics and intended use had the advantage of rendering superfluous the need for biotechnology-specific legislation; regulation could be carried out by existing agencies under existing (if sometimes modified) statutes, with product-use determining agency jurisdiction. Avoiding the legislative route would, it was believed, afford flexibility to the regime, which, in turn, would facilitate keeping pace with the rapidly advancing scientific and technological frontiers.

This approach has worked well enough in the case of biopharmaceuticals; with the risk assessment process more advanced for industrial than for environmental applications of biotechnology, and the health and safety stakes lower, the FDA has been able to regulate along more or less conventional lines, although bioproducts are evaluated on a case-by-case basis (a practice that has increased both time lags and the demand for capital and human resources on industry and the FDA itself).

In the area of environmental release, U.S. policy has met with considerably less success; with critical scientific questions remaining unanswered and quantitative risk assessment still very uncertain, the inadequacies of existing legislation have been blatant (particularly under the Toxic Substances Control Act, which authorizes the Environmental Protection Agency to oversee recombinant microorganisms, but was designed with chemical substances in mind). Caught between legitimate scientific concerns and pressures from the Administration and industry, both the EPA and the U.S Department of Agriculture (USDA) have been hard put to come up with rules on deliberate release (indeed, in the case of the EPA, to determine the scope of such rules). Moreover, since agency jurisdiction is determined by intended product use, many products fall under the regulatory responsibility of more than one agency; for companies this means multiplying filings and meeting differing sets of requirements. Regulation presently proceeds on an *ad hoc* basis and within the confines of small-scale tests. Meanwhile the advantages of flexibility have been more than offset by obstacles linked to regulatory unpredictability and lack of clarity, and to overlapping bureaucracies, with the ag-bio industry paying dearly in time and resources.

EC regulatory policy stands in rather stark contrast with that of the U.S. Deeming it necessary to oversee not only the products of biotechnology but the processes by which they are produced, the Community has combined a vertical (application-specific) and a horizontal (technology-specific) approach to regulation. Moreover this approach has been embodied in community-wide legislation, whereby once the EC Council adopts biotech directives (of which four have been approved to date, with many more in the pipeline), member states must enact them into national law.

By opting for umbrella, community-wide legislation, the EC has given priority to interagency consistency and cross-country standardization as ways of optimizing the regulatory process and, specifically, of leveling the competitive playing field among EC member states and avoiding intra-community trade barriers. Thus, for instance, although regulation of environmental release is clearly more stringent than in the U.S., the European directive provides a uniform and binding set of rules covering everything from notification preparation through small-scale field trials to the marketing of recombinant products (cf. Journal officiel des Communautés européens, 1990)

This being said, there are signs that, in its preoccupation with international competitiveness, the EC is also sensitive to elements of the U.S. regulatory philosophy. Thus, for instance, in its document "Promoting the Competitive Environment for the Industrial Activities Based on

Biotechnology Within the Community" (April, 1991), the European Commission simultaneously reiterates the necessity for member-state enactment of directives approved by the European Council, and speaks of "constant assessment of the appropriateness of existing and proposed legislation", a clear step in the direction of regulatory flexibility. It is, furthermore, believed by some that stringent directives on the contained use and deliberate release of genetically engineered organisms may undergo just such a reassessment (J.Hodgson, 1991).

The political process in which biosafety regulation is immersed is also effecting both the shape of regulatory regimes and the rate of biotech innovation. Above and beyond the conflict and bargaining process that is part of rule-making and that involves lobbying by interested parties, regulatory politics brings into play interagency jurisdictional turf wars, with industry often caught in the middle[11]. But more disturbing still are the high-level power politics that are plaguing the regulatory system, particularly in the U.S., where accusations of secrecy, high-handedness and interference have repeatedly been leveled against executive-appointed committees charged with coordinating regulatory activities. As recently as July 1991, it was reported that members of Congress are debating whether to request a Government Accounting Office investigation into alleged "'White House interference with science advice to the agencies'"; as a congressional staffer out it, it's "'a matter of who's in charge of developing scientifically based regulations - political appointees or scientists'" (J.L.Fox, 1991). Externalities of this sort cannot but increase regulatory inefficiencies (even when they are generated by those who invoke the "invisible hand").

iii. Human, material and budgetary resources. In the U.S. and probably a number of other countries, a lack of qualified regulatory personnel, particulary top-level and entry-level scientists and physicians, is linked to competition for human resources from the private sector and even academia, which offer more attractive salaries and working conditions. In the U.S., deep cuts in agency funding that have accompanied laissez-faire policies since the early 1980s have fed into this problem. Budgetary restrictions are also related to lags in up-to-date laboratories and equipment and to the inability to computerize the review process. As the number of product applications continues to increase, regulatory delays stemming from personnel and infrastructural shortages may well offset gains in lead times due, among other things, to the standardization and routinization of regulatory procedures.

iv. Public acceptance

There is a growing consensus within both government and industry that a key element in

determining the ultimate success of commercial biotechnology is the capacity to create a climate of public trust. With respect to this problem, an OECD report puts responsibility squarely in the lap of government, noting that "[i]n cases where the public has shown concern about a technology, scientific acceptability is a necessary, but not sufficient condition of acceptance. When a gap between acceptability and acceptance appears, it will be a goal of public policies to attempt to close it." (OECD, 1989)

Regulatory bodies obviously play a critical role in securing (or failing to secure) public trust, and risk assessment is indissociably linked to questions of public policy. This is particularly so in the sensitive area of environmental release; agencies mandated to oversee the environmental applications of biotechnology already bear the legacy of radioactive waste linked to technological innovations in the nuclear industry, and toxic waste generated by the chemical industry. This legacy undoubtedly contributes to the fact that environmental agencies in many countries tend to view anything associated with biotechnology with extreme caution.

But environmental release is not the only area in which regulators must bear in mind both earlier failings and the credibility problem those failings have helped to create. As recombinant products such as engineered tomatoes begin to enter the food chain, new concerns will become the focus of public scrutiny and debate, partially because of past difficulties. The latter include the banning of the hormone diethystibestrol after 25 years, because of carcinogenic chemical residues discovered in treated meat, and, more recent public outcries involving pesticides. As late as 1990, the U.S. EPA recognized that "legal limits on chemical residues for most pesticides in use before 1985 are based on inadequate information" (M. Burros, 1990). Public confidence in the FDA will certainly not be boosted by ongoing investigations into the Agency's alleged role in covering up concerns about animal health and, possibly, human safety, in an attempt to accelerate the approval of recombinant bovine growth hormone (bGH).

As regards trust building, undoubtedly the most important thorn in the side of regulatory bodies (and industry) have been the highly visible environmental and other public interest groups, whose use of the media has been effective in arousing public biosafety concerns. Among the tactics used by such groups are the sabotaging of ag-bio field tests, as well as petitioning and even suing government and industry. In the US, litigation is a particularly effective means of creating regulatory delays, even when cases are lost. And the sole issue of liability coverage presents a potentially serious threat to small, cash-poor biotech companies.

Another public policy issue that has generated considerable public reaction is that of

socioeconomic impact, particularly when agricultural productivity enhancers are involved. In the by now notorious case of genetically engineered bGH, concern that inexpensive, hormone-induced milk would drive small farmers out of business -- as well as skepticism about the effect of bGH on dairy cows and the milk's safety for human consumption -- has provoked strong reactions on both sides of the Atlantic, with public interests groups exerting considerable pressure on government and industry. With regulatory agencies traditionally mandated to assess drugs on the basis of three scientific criteria (safety, quality and efficacy), the *de facto* introduction of a needs criterion, the so-called "fourth hurdle", into the product approval process, has contributed to keeping bGH off the commercial market. In the EC, furthermore, implicit regulation by public interest groups and farmer lobbies has undoubtedly played a role in the drafting, by the Agricultural Directorate, of legislation that, if adopted, would make socioeconomic needs assessment part of the approval process.

As biotechnology gets more deeply involved in areas such as human gene therapy and the engineering of farm animals, sensitive bioethical questions are certain to provoke yet further public reaction, creating new regulatory externalities.

The preceding observations well illustrate the more general problem of making ends and means meet in regulatory policy-making and implementation. Stated goals of fostering the innovative process, commercial interests and national competitiveness are undermined by a host of regulation-related rate-limiting barriers.

With the exception of fast-track and/or parallel track review for biotherapeutics aimed at life-threatening diseases, long lead times and the associated costs and uncertainties created by regulatory externalities are plaguing the U.S. biopharmaceutical industry. Following years of regulated clinical tests, FDA approval of genetically engineered drugs still takes an average of 34 months, with the result that only 13 drugs have been approved, while over 100 are caught up in the final pipeline (not to speak of some 800 other bioproducts, including diagnostic tests and drug delivery systems). This in turn has many companies planning initial clinical trials abroad (Gibbons, A., 1991)

Ag-biotech firms face even greater regulatory delays. As of May 15 1991, applications for environmental release of some 156 genetically engineered plants and 28 genetically engineered microorganisms had been approved or were under review by the USDA and the EPA (The Gene Exchange, 1991), but almost all these applications concern small-scale field trials, and

permits continue to be issued on a case-by-case basis. In the absence of overall rules for large-scale testing, and given the pressures exerted by public interests groups, it is likely that most engineered bioproducts (particularly microorganisms) designed for release to the environment will remain in the regulatory pipeline for some years to come. Under the circumstances it would not be suprising that, as many believe, some companies seek to accelerate the testing process by conducting early trials in countries that do not regulate deliberate release, although this does not solve the problem of meeting home country criteria, and involves the risk of potential public image fallout.

In both the pharmaceutical and agricultural application sectors, regulatory barriers give a competitive advantage to large established corporations, which have greater financial staying power and regulatory experience than dedicated biotech companies. However even the most powerful corporations can experience financial strain when the approval of heavily funded products becomes a protracted and precarious affair. For instance, Monsanto has sunk an estimated $250 million into recombinant bGH and is spending some $58 million annually to keep prepared for the eventual launch of the bovine growth hormone and a related porcine growth hormone (J.F.Siler, 1991); meanwhile, FDA approval of bGH appears to be increasingly unlikely.

Finally, it should be noted that regulatory barriers play a critical role in determining not only the timing but also the direction of innovation in biotechnology; this is true both across and within application sectors. One of the reasons that commercial ag-bio lags behind biopharmaceuticals is that the scientific basis for risk assessment is less advanced. Similarly, within agricultural biotechnology, controversy over deliberate release (especially of GEMs) and recombinant products entering the food chain has many companies, both small and large, re-directing R&D towards more readily acceptable products, while some existing projects have been put on the backburner or simply dropped.

5. Intellectual property rights

Since patent approval does not pay off until the sale of a product has also been authorized, lengthy patent delays are considerably less damaging to industry than regulation-related time lags. Nonetheless long patent-issuance lead times do constitute an entry deterrent barrier; among other things, they expose unprotected technologies, impact the competitive position of companies and products and increase costs. (G.S. Burrill and K.B. Lee,Jr.,1990)

Between April and December 1988, U.S. patent pendency periods for biotechnology averaged 29.4 months, as opposed to 21.0 months for all patent issuances/rejections. By application sector, periods were the shortest and issuances the most numerous for equipment (26.0 months/401 patents) and the longest for genetic engineering (39.2 months/36 patents). During the same period, the backlog of biotechnology patent applications grew at a 19 percent rate (5,200 to 6,200). (U.S.GAO, 1989).

The reasons for patent issuance time lags are, in several ways, strikingly similar to those causing long regulatory time frames. In both instances, the complexities, newness and rapidly advancing frontiers that characterize biotechnology create learning curve-related delays and shortages of senior examiners qualified to train junior staff. As in the regulatory arena, the best human resources are siphoned off by the private sector, although, in the U.S, government has recently undertaken to redress this situation by granting the Patent and Trademark Office special engineering salary rates; furthermore, industry itself has shown interest in addressing staff shortages, with the Industrial Biotechnology Association setting up its own Institute for training biotechnology examiners.

But patent issuance is not the only problem linked to intellectual property externalities. Loopholes, ambiguities, and unanswered questions about patent scope, leave plenty of room for legal challenges, particularly in the U.S. where, for instance, it is possible to hold a product patent without having rights over the processes involved in making the product. Similarly, different patents can cover different aspects of a given product or process, or, conversely, a single patent can, in some cases, cover the application of an idea to different species Among unanswered and controversial issues concerning patent scope: should a patent's claims ever encompass progeny? (J.H.Barton, 1991; G.S. Burrill and K.B. Lee, Jr., 1990).

When the threat of costly and time-consuming litigation is added to patent-issuance delays, it becomes understandable that many pharmaceutical companies seek the advantages of orphan drug status, which offers 7-year exclusive marketing rights, costs nothing beyond the preparation of the submission, and can be granted within as little as thirty days after filing. Furthermore, an orphan designation can be established for just about every bioproduct derived from the mammalian or human genome, i.e. the area where patenting has proven the most problematic (J.G.Thoene, 1991). Companies are also increasingly turning to cross-licensing as a less expensive, less uncertain and less drawn-out alternative for maintaining market position.

Cross-country patenting differences, both procedural and substantive, also impact the timing of

market entry and decisions as to which markets to enter. In Japan, patent approval time lags are even greater than in the U.S., with foreign applications for biopharmaceuticals sometimes held up in the Japanese Patent Office for years before first actions are made, and during which time these same products are being sold by Japanese firms. Similarly, many countries use a "first to file" criterion for awarding patents, while in the U.S. patents are granted on a "first to invent" basis; this makes it more difficult to protect rights in the U.S. and in cross-border filings.

Substantive limitations on the patenting of bioproducts also vary. For instance the Japanese patent is so narrow in scope as to be easily circumvented; this constrasts with U.S. and European practices of offering broad coverage. Likewise, many countries do not offer protection for recombinant microorganisms, plants and animals and/or limit the ability to exercise patent rights, as through extremely broad compulsory licensing schemes. (L.J Raines, 1991). All of these considerations obviously play an important role in the international strategies of companies.

6. Competitiveness

In the last analysis, the commercial success of biotechnology depends not only upon its inherent advantages, of which there are now many examples, but also upon the relative competitiveness of its products and processes. A notable exception to this rule concerns instances where the technology has generated totally new products or has overcome absolute limits to the availability of inputs (UNIDO, 1991). This latter situation applies, among others, to the production of insulin and human growth hormone, which until recently involved the costly and time-consuming tasks of drawing and then processing minute quantities of extracts from large amounts of animal tissue or, in the case of H.G.H., from human cadavers.

Some of the more important bottlenecks, scale factors and barriers interfering with competitive market entry have been identified in the preceding pages. These include gaps in basic and applied scientific knowledge, heavy research-related costs, scale-up inefficiencies, expensive and protracted regulatory procedures, patent litigation, skill shortages, and a sometimes unreceptive public.

Additional factors that negatively impact relative competitiveness and the overall timing of introduction and rate of diffusion in biotechnology, are rooted in organizational, institutional and managerial inefficiencies, as in the case of the U.S. health-care system (F.Sercovich and M. Leopold). With medical costs now accounting for 12 percent of the country's gross national

product, pharmaceuticals are under increasing pricing pressure from the public and private health insurance system, and reimbursement issues are rapidly becoming a major new hurdle for the industry. Although biopharmaceuticals tend to be treated with more latitude than traditional drugs, their coverage by the insurance industry (which is crucial to their success) will be increasingly linked to cost-effectiveness criteria. Cost/benefit analysis will probably raise questions about many products on the market and in the pipeline --t-PA and EPO are already under scrutiny, and companies that do not or cannot afford to factor such analysis into their clinical-trial strategies will be at increased risk. Furthermore, in those instances where cost-effectiveness does afford a competitive advantage to biopharmaceuticals, the question remains as to how the U.S. economy is going to absorb the costs of large-scale marketing.

The rate of product development is also affected by difficult and inconsistent access to capital. This is particularly clear in the case of biopharmaceutical and ag-bio applications, which have the longest development lead times and are submitted to the the full rigors of biosafety regulation, and with regard to small- and medium-size firms, which have the same up-front investment needs as larger companies, but not the revenues to support them nor, it follows, the capacity to wait out lengthy payback periods.

Company strategy also influences biotechnology's relative competitiveness and the timing of product introduction. Generally speaking, established pharmaceutical and agrichemical corporations do not seek to block the new technology - on the contrary, it is these companies that tend to take control of biotech products as these approach market, and that are usually in the forefront in the race to reach the marketplace (cf. F. Sercovich and M. Leopold, forthcoming). But in those instances where bioproducts are actually competing with profitable established markets, corporations may use biotechnology to extend the life cycle of existing products, as in the case of pesticide-resistant plants being developed to work with new generation pesticides. Such strategies can slow advances in certain areas of biotechnology, but they cannot actually bring progress to a halt; nor is it in the long term interest of corporations to do so, given the erosion of their market positions. This is why, for instance, the same companies that are developing pesticide-resistant plants to accompany their new generation pesticides are also working on pest-resistant plants and biopesticides.

As long as, and to the extent that, biotechnology does not secure a clear competitive advantage over conventional products and processes, its future trajectory remains uncertain. Gaining this advantage is likely to be an uneven process, since the weight of entry deterrent barriers varies across application-sectors and user-industries, and according to company size, country,

learning curve- and other time-related factors, etc. Unanticipated events such as radical scientific and technological breakthroughs or significant shifts in relative prices, can dramatically enhance the relative competitiveness of biotechnology, but, here again, changes will not impact all sectors at the same time and/or to the same degree.

The competitive potential and diffusion rate of specific applications is not easy to predict, and there have been several surprises to date. In the case of chemicals, particularly commodity chemicals, the impact of biotechnology has fallen far short of initial forecasts, partly because of major technical limitations on the technology's use for chemical production, partly because of underestimations as to the relative competitiveness of organic chemistry and highly optimized chemical manufacturing processes (R.L.Hinman, 1991). However with major biotechnological inroads presently being made in the area of speciality chemicals - including the highly productive "farming" of biopolymers, a field in which growing manufacturing efficiences will allow increased competitiveness *vis à vis* oil-based plastics (G.McWilliams, 1991) - it is difficult to anticipate the future overall impact of biotechnology on chemical processing. Similarly, in the area of pollution prevention, several biotechnology-based projects are presently being developed, but it is too early to determine how the new techniques and products will fare in the regulatory arena, and in terms of relative costs, etc.

Competitive dynamics can also be redefined by the introduction of rival technologies or by synergistic approaches to product development. A previously-cited example of this latter case is that of rational drug design, whereby genetic engineering is used to improve conventional pharmaceutical R&D. Whether this industry-driven approach, in turn, proves competitive depends in part on newly created challenges; among other things, the synergistic use of biotechnology, protein crystallography, computer modeling and chemical synthesis requires a highly coordinated and successful effort at scientific sharing, and the associated interdisciplinary managerial skills.

Although many factors are still preventing biotechnology from fully realizing its competitive potential and although present time lags may in and of themselves open the door to an altered competitive dynamics, rapid advances at the scientific and technological frontiers, a steady stream of secondary innovations, and the inevitable shortening of lead times keep alive expectations that biotechnology will indeed become a major social and economic force in the coming century. One recent example of such promises involves a double milestone in the attempt to find a substitute for blood: the production of human hemoglobin in transgenic pigs and a breakthrough technique for purifying the hemoglobin. If proven safe for human transfusions and

cost competitive, this blood substitute, which has several inherent advantages over donated blood, could meet an important need of society.

7. LDCs: lessons to be learned

In developing countries, as in the advanced industrial economies, the real-world difficulties of entering biotechnology are in the process of superseding early hype. The shedding of illusions is undoubtedly requiring that much greater an effort that much has been made of biotechnology's potential for solving economic and social ills of LDCs, and that the technology was heralded by many as being particularly appropriate for leap-frogging (F.Sercovich and M.Leopold, 1991).

This is not to say that LDCs cannot or should not enter biotechnology -- in fact a considerable number of them already have entered --, but the scale, scope, timing and success of the undertaking, as well as the actual entry scenarios and application sectors, will depend, in good part, upon the capacity of the various countries to deal with the sorts of obstacles to commercialization identified in the preceding pages.

These obstacles are, to be sure, not the only factors that will determine the future of biotechnology in LDCs. Indeed, that future will result from the interplay of a large number of variables, including, on the country level, threshold factors such as market size, industrial infrastructure, availability of financing, scientific, technological and manufacturing skills and capabilities, as well as national science and industrial policy, and linkages between the public and private sectors. Furthermore, much will hinge upon developments in the industrialized countries, where the new biotechnology came into existence, and where its trajectory is being defined. Thus, for instance, the rate at which multinational corporations seek to export biotech products, technology or activities to LDCs will depend, among other things, on various aspects of company strategy and on conditions that prevail on home markets and in other industrialized economies.

These and other considerations notwithstanding, it is imperative that LDCs pay due attention to the question of gaps, bottlenecks, scale factors and entry barriers. The countries that are presently leading the way in biotechnology have understood that successful market entry is closely linked to correctly identifying and overcoming these obstacles, and they are acting correspondingly; it is incumbent upon LDCs that seek to compete to do as much.

Footnotes

1. Established in 1988 as a bilateral group under the auspices of the U.S.-Japan Business Council and the Japan-U.S. Business Council, the Forum on Biotechnology decided in 1990 integrate the European Senior Advisory Group on Biotechnology. In 1991 the Industrial Biotechnology Association of Canada also joined the Forum, the U.S.and Japanese memberships of which have been passed on to the respective industrial biotechnology associations. In 1990 the original Forum issued a report on the "harmonization of the scientific principles and procedures 'underlying the regulations related to biotechnology".

2. Declining productivity has been linked to stringent regulation and a decrease in returns to trial and error screening techniques used in traditional drug development. Safety and efficacy testing is said to account for some 60% of the cost of developing new drugs (F.Sercovich and M.Leopold, 1991).

3. In many instances acquisition is actively sought by startups, and some of the latter are actually founded with the objective of being sold.

4. R&D threshold factors are not the only barriers that strategic alliances help to overcome, particularly in the case of biotech startups; in addition to being a major source of capital, these partnerships can offer support in the areas of production and marketing/distribution capabilities and regulatory expertise. Dedicated biotech firm that are engaged in several partnerships (as most are) gain the additional advantage of tying up their assets in such a way as to make them less vulnerable to takeovers.

5. Average drugs prices are much higher in the U.S., where they are fixed by industry, than in Europe, where governments usually negotiate prices. American consumers are thus subsidizing worldwide R&D. (G.Kolata, 1991). Market size notwithstanding, pricing flexibility is an important reason for non-U.S. firms to seek a strong U.S. presence and for U.S. firms to offset relatively lower overseas returns. This situation can be expected to change somewhat as cost-containment issues begin to be adressed (cf. infra on competitiveness).

6. This explanation has recently been stood on its head in a draft U.S. OTA report to Congress, which holds that the industry's $221 million estimate cost of developing a new drug is an arbitrary figure aimed at justifying exorbitant prices. (M. Freudenheim,1991). With returns on sales of over 20% and profit margins three times those of most other major U.S corporations in 1990, pharmaceuticals are indisputably the most profitable U.S. industry. In fact, profitability is often cited as one of the major reasons why the biotech startups choose to go into pharmaceuticals rather than other application sectors. Industry sources also link high relative prices to the fact that U.S. law allows for quick release of inexpensive generics when patents lapse - as will be the case for many major products in the coming years - , with no new drugs to pick up the slack. In many instances acquisition is actively sought by startups, and some of the latter are actually founded with the objective of being sold.

7. Established pharmaceutical companies are keeping a close watch on developments at rational drug design startups, with some already engaging themselves financially. Such cases include Japan's Chugai Pharmaceutical Co.'s buying heavily into Vertex, a cutting-edge drug-design company , as well as a recently concluded strategic alliance between Schering-Plough and Agouron Pharmaceutical, whereby the former is investing $6.5 million into the latter in exchange for non-exclusive rights to Agouron's technology and expertise in determining the molecular structures of proteins. Together the companies will attempt to design anti-cancer drugs targeting the RAS protein (J.O'C.Hamilton *et al*, 1991; Bio/Technology, June 1991).

8. These include the exploitation of inaccuracies in the diagnosis of hGH deficiencies, heavy financing of the Human Growth Foundation, funding and courting researchers in pediatric endocrinology.

9. The President's Council on Competitiveness Report (cf supra) has discretely admonished such practices by recommending that the FDA "develop administrative proposals to address concerns about the definition of 'disease' used in the program to avoid overextension of the program to treatments that are not 'orphan'. (p.18)

10. This marketing success story may yet meet an unhappy ending; long-term efficacy of the drug (i.e. increased adult height) has not been clinically proven in the case of non-hGH-deficient children, nor have potential long-term health risks to this population been excluded.

11. In the U.S., jurisdictional disputes concern not only the agencies themselves, but the various Congressional committees mandated to oversee them and to interpret statutory reach. In the case of the EC, interbureaucracy conflicts may involve up to a dozen directorates potentially involved in regulating the work of biotech companies, and the above-mentioned directives on the contained use and deliberate release of genetically modified organisms are seen, in many quarters, as an attempt by the Environmental Directorate (DGXI) -- author of the directives -- to force other Directorates to either adopt its rules or to forfeit any control over regulation in these areas.

In certain countries, a second jurisdictional bottleneck exists in the form of a two tier regulatory system. In both the U.S. and Germany, federal-level oversight is paralleled by state/Land regulation, although in Germany this will change as EC-level legislation is implemented, and the U.S. Adminstration, partially under pressure from industry, is calling for the elimination of state and local laws.

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