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Commentary

Emerging Trends in Biotechnology: A Perspective from the Pharmaceutical Industry[1]

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I wish to address the emerging trends in biotechnology regulation from the pharmaceutical industry's perspective on this most important issue. As you know the well over 100 members and research affiliates and associates of the Pharmaceutical Manufacturers Association (PMA) have been practicing the art of biotechnology for a number of decades in order to produce such products as vitamins, antibiotics, steroids, and more recently, insulin, interferon, and human growth hormone. Although biotechnology or the use of organisms such as bacteria and yeast to produce a useful, beneficial product is an ancient art, the use of recombinant DNA techniques and cell hybridoma techniques has given rise to a "new" biotechnology which brings with it several new problems and concerns. Let me present some background on how biotechnology is practiced by the pharmaceutical industry today and outline what issues and concerns I see for the "new" versus the "old" biotechnology and even how the two interrelate. The use of classical methods of tedious and expensive strain selection with the use of induction of mutations through chemical or radiation techniques is yielding to the more efficient and elegant, almost scalpel-like, precision of introducing or highlighting a particular gene coding for a targeted product through recombinant DNA and cloning techniques. Products that would have been difficult to produce are now becoming commonplace.

The PMA recently commissioned OMEC International to conduct a patent study to determine the number of U.S. biotechnology patents issued in 1986. They reported that 1232 biotechnology patents were issued, an increase of 14% over 1985; 673 or 55% of the patents issued were in the area of pharmaceutical/health-care products. I had occasion to analyze further OMEC's data and noted that of the 166 pharmaceutical/health-care patents issued to PMA members, 38 fell into the new biotechnology category (see Table I). The remaining 128 used "classical" biotechnology techniques. A further breakdown analysis showed that most diagnostic products are being developed through biotechnology but that therapeutics such as vaccines and antineoplastics are coming up fast.

The trend for products using the newer techniques is clearly upward. Mary Ann Danello of the FDA recently reported at a conference on biotechnology regulation that the FDA has already "approved or licensed almost 200 monoclonal antibody-based diagnostic kits and half a dozen each of therapeutic drugs and rDNA probes for infectious agents." She also reported that many more are in the pipeline, with an additional 150 drugs alone currently in clinical trials.

Table I. Analysis of 1986 U.S. Pharmaceutical/Health-Care Patents

	Area of research		
Research area	Classical	New biotechnology	Total
Antibiotics	37	1	38
Antivirals	—	3	3
Vaccines	4	4	8
Antineoplastics	11	4	15
Other therapies	45	7	52
Diagnostics	31	19	50
Total	128	38	166

The PMA has reported that in 1986 four new biotechnology products were introduced by PMA members. These include the following:

two α-interferons for hairy-cell leukemia (Intron A, Roferon-A),

one hepatitis B vaccine (Recombivax HB), and

OKT-3 monoclonal antibody for kidney transplant rejection (Orthoclone OKT3).

These products augment two bioengineered products of earlier years, namely, Humilin and HGH. These new therapeutics represent a number of firsts for the pharmaceutical industry.

The regulation of the pharmaceutical industry by the FDA has been a long and evolutionary one with good dialogue as guidelines and standards are set in place. The FDA is presently a mature regulating agency.

The FDA's strategy of regulating products, and not the processes used to produce them, has put products derived from new and old biotechnology on an equal footing. To improve the review process, the FDA has announced that it is adapting biologics advisory committees to meet the needs of biotechnology product review. For example, Genentech's tissue plasminogen activator NDA was evaluated by the FDA's Cardio-Renal Drugs Advisory Committee. The FDA is updating its regulatory policies in order to adapt to the manufacturing methods of biotechnology companies, which were advised to be aware early on of the possibility of product alteration that can occur during processing. Factors that control product alteration include the following.

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1. The producing organism: genotype, strain, seed stock, vector, and gene sequence.
2. Production: fermentation conditions, plasmid copy number and stability, assays, yields, and reproducibility.
3. Extraction: cells or medium and effects on product.
4. Purification: size, charge, hydrophobicity, affinity, and especially MABs.
5. Identity: amino acid composition, C- and N-end terminals, sequence, and posttranslational modification, e.g., glycosylation, biological activity.
6. Purity: contaminants, e.g., DNA, bacterial proteins, and residual monoclonal antibodies.

Product alteration during processing is a key concern. It would appear at first glance that the development of pharmaceutical products using the new biotechnology versus the old biotechnology would not require different or unique regulations but would instead be regulated within the existing framework of the government regulatory agencies and that the new biotechnology industry would benefit from the earlier experiences the FDA had in regulating the old biotechnology products.

The PMA's board of directors recognized the importance to the industry of this emerging technology when it created the new membership category of research affiliate. Small biotechnology companies developing new drugs were given the opportunity to join the science and technology sections of the PMA, which deal with the research and development, quality control, and production of drug products. Even before that, the science and technology sections of the PMA recognized that the problems unique to biotechnology, here limited generally to recombinant DNA and hybridomas, might require attention not afforded by the existing section structure. A committee of section representatives was formed to assure exchange of information on problems, but each section, by its expressed wishes, continued to deal with problems that fell in its purview. Because the FDA had taken a reasonable approach to the review and approval of recombinant DNA-produced insulin and diagnostic products based on monoclonal antibodies, there has, until recently, been no pressing need to consider any new mechanism.

However, recent developments, both domestic and international in areas unique to biotechnology dictated a change in our approach. One example is when the U.S. State Department sent a delegation to the Organization for Economic Cooperation and Development (OECD) to discuss international guidelines for the regulation of biotechnology. Other examples are the recent court decision that stopped the deliberate release of "modified organisms" into the environment under a National Institutes of Health (NIH) program, with some indication that the injunction might apply to commercial activities, and the EPA's specific provisions for other regulatory agencies by invoking its broad mandate, specifically the Toxic Substance Control Act. These activities could all have an impact on the pharmaceutical industry. For example, live polio vaccine (i.e., Salk oral vaccine) and other live attenuated virus vaccines could easily be construed as falling under any regulation relating to modified organisms and, with a little extrapolation, to "deliberate release" issues. There is considerable congressional interest in, although apparent little understanding of, problems of biotechnology, genetic testing, and related activities. It was concluded that there undoubtedly would be efforts to develop national standards or regulations.

The PMA board therefore created a Biotechnology Advisory Committee to develop a long-term agenda on biotechnology. The committee formed two important subcommittees to review biotechnology regulations, the EPA Subcommittee and the FDA Issues Subcommittee. One issue the FDA Issues Subcommittee examined was the review process of drug products made through biotechnology and by other methods.

Although we have seen a number of new biotechnology products introduced over the last few years and we see on the horizon more in the pipeline, costs for drug development remain high. On average, it costs well over $100 million to bring a new drug through discovery, chemical testing, development, and FDA approval to begin marketing. The cost has increased sharply in recent years, due mostly to the increasingly intricate nature of modern research and, especially, the highly sophisticated equipment required. To develop products it still takes approximately 10 years to move a drug from discovery to marketing. The FDA's workload and backlog for new drug applications have increased (64 in 1985 vs 73 pending in 1986). The FDA approved 20 new drugs [new molecular entities (NMEs)] in 1986, down from 30 approved in 1985 and 22 in 1984. The four biotechnology drugs I mentioned earlier are included in the 20. Thus, we are still seeing a long and expensive review process for the introduction of new drugs including those derived from new biotechnology. In 1986 the 20 NMEs averaged 34 months for FDA review, compared to 32 months in 1985. The PMA's FDA Issues Subcommittee has been meeting with the FDA on a regular basis to improve the drug review process from both ends. The establishment of special FDA review committees may help, as well as other action (computerized NDA, upgrading scientific expertise, etc.).

In our continuing dialogue with the FDA we see a number of issues regarding new biotechnology products coming to light. Among them are the following:

1. analytical methods applied to drug substances produced by rDNA methods, e.g., criteria for setting product specification (purity/?/contaminants);
2. chemical microheterogeneity in macromolecules and the extent of batch-to-batch variation acceptable to the FDA;
3. procedures for approval of changes in production methods (vector/host system);
4. acceptability of reprocessing; and
5. measurement of foreign contaminants such as host-cell proteins, DNA/RNA, and pyrogens (lipopolysaccharides), related substances such as clips (aggregates of desired protein derived from isolation, purification, formulation) and heterogeneity of desired protein.

In addition to FDA regulation, what do we see on the horizon with other regulatory agencies?

As many of you already may know, the Office of Science and Technology Policy established the Biotechnology Science Coordinating Committee to develop a coordinated framework for the regulation of the biotechnology

industry (published June 26, 1986). Each agency produced separate policy statements: the FDA, EPA, USDA, etc. All said that they will implement policies to operate in an integrated fashion. Our advisory committee supported the concept of oversight for biotechnology research and development and suitable regulatory approval for biotechnology-derived products. We believe that the framework can be effective if it is implemented utilizing the *best available science* as the common basis for decision making. And I want to emphasize *best available science*.

The major issues and problem resolution have been left to the EPA, e.g., definitions of pathogen, environmental release. The EPA has created a Biotechnology Science Advisory Committee to develop further definitions of pathogen and environmental release. How the final definition regulation will be approached will have major effects on the development of biotechnology products in this country. There are some legitimate concerns.

On May 28 of this year, the Office of Technology Assessment released a report on *Public Perceptions of Biotechnology* based on a telephone survey of 1300 adults by the Louis Harris Agency. The OTA said, "The survey finds that while the public expresses concern about genetic engineering in the abstract, it approves nearly every specific environmental or therapeutic application. And, while Americans find end products of biotechnology are attractive, they are sufficiently concerned about potential risks, that a majority believes strict regulation is necessary either by a government agency or some nongovernment scientific group." The OTA also pointed out that "unjustified biotechnology fears seriously impeded drug development." Furthermore, "the public believes that the federal agencies are distinctly less able than university scientists to assess potential risks; moreover, in disputes between federal agencies and environmental groups over risk statements, the majority of the public says it is *inclined to believe the environmental groups*."

The use of rDNA organisms, e.g., *B. subtilis, E. coli,* and yeast, to make a wide variety of products has been in practice over a decade. The pharmaceutical industry has adhered to the NIH–RAC guidelines on the use of these organisms. Recently, the guidelines for these organisms have been clarified and relaxed through a proposal submitted by FDA Commissioner Frank Young. These clarifications will allow the most cost-efficient preparation of protein products made with these organisms. All the plants used to produce protein products followed the more stringent NIH BL 1-LS (Biosafety Levels 1—Large Scale) guidelines. In a recent report, A. D. Little states that for all biosafety levels (BL 1-LA through BL 3-LS) the following are required:

1. a closed system (vessels and pipes or biosafety cabinet) wherever viable organisms are present,
2. a validated procedure for inactivation of cultures prior to removal from the system.
3. closed systems for collection and addition of samples and other materials,
4. sterile filtration or incineration of exhaust gases, and
5. a validated sterilization procedure before opening the system (for maintenance or other purposes).

As the environmental groups focus on the issue of environmental release, and many are focusing on the state levels (e.g., New Jersey and Texas have bills pending on the books), the record of safe experience with biotechnology and, in particular, the use of the above organisms may become obscure, and what was once regulated through sound scientific principles may be regulated by public perceptions which overflow and backflow over an existing and established industry. The question for all of us to consider is this: Will the biotechnology industry be regulated utilizing the best available science and through the development and evolution of a coordinated framework of existing federal agencies or will public perceptions change, creating a myriad of special federal and state agencies slowing down existing and future development because of the need to go through a maze of bureaucracy? To quote Abraham Lincoln, "Public opinion is everything."