

MAMMALIAN CELL CULTURE: WORLDWIDE ACTIVITIES AND MARKETS

As biotechnology comes to market, the number of products manufactured by mammalian cell culture—as opposed to bacterial or yeast systems—is on the rise. Many of these products, especially those for human and animal health care and diagnosis, will reach the market in the next three years (Table 1). As the markets grow, the contribution of mammalian cell culture as a production technology will also increase, accounting for billions of dollars in product sales. Growing markets for mammalian cell culture-derived products will also contribute to expanded, though smaller, markets for bioreactors, culture media, and media additives.

Products OF Cell Culture Technology

Worldwide market projections for key biotechnology product areas in 1991 are given in Table 2. It should be noted that these numbers encompass a variety of production technologies; cell culture is not the exclusive means of manufacture.

The most important product areas for mammalian cell culture currently are monoclonal antibodies and vaccines.

Monoclonal antibodies are used today largely in *in vitro* diagnostic tests and, to a lesser extent, in purification and research. In addition, imaging and therapeutic applications are being developed. In the diagnostic area, monoclonals compete with existing tests composed of polyclonal antibodies, cultures, and serologies; in the future, monoclonals will compete with DNA probes, whose development time has been slower.

Monoclonal antibodies are widely applicable to animal care, as well as human medicine. Over 203 companies are developing veterinary diagnostics. Although monoclonal antibodies will probably not command a large share of the total market for veterinary diagnostics, the overall potential, were every animal in the world to receive each available test, exceeds \$50 billion. For at least 19 of the common diagnostic tests, the world market potentials exceed \$1 billion each. Even though only a fraction of this potential may be realized, it is clear that low-cost veterinary tests will result in substantial worldwide markets.

Vaccine markets are substantial, as well. Vaccines for veterinary applica-

TABLE 1. Expected Dates of Product Introduction for Selected Products that can be Made by Mammalian Cell Culture

Product	Expected Date of Introduction
Tissue Plasminogen Activator	1987
Hepatitis B Vaccine	Launched*
Superoxide Dismutase	1988-89
Factor VIII	1988-89
Atrial Natriuretic Factor	1990
Lymphokines	
Interferons	Launched**
Interleukins	1988
Tumor Necrosis Factor	1989
Colony Stimulating Factors	1987-88
Erythropoietin	1988
Human Growth Hormone	1986
Epidermal Growth Factor	1988-89

*Merck received U.S. and Far East approval in 1986, and SmithKline Beckman received regulatory approval in Belgium in late 1986, and Switzerland and Luxembourg in 1987.

**Alpha interferon has already been launched.

TABLE 2. 1991 World Markets by Categories for Products that can be made with Mammalian Cell Culture

Product area	Projected 1991 World Market (\$ millions)
Diagnostics	6,500
Vaccines	5,200
Hormones	4,900
Lymphokines	1,750
Monoclonal antibodies	1,700
Other products	3,040
Epidermal growth factor	
Superoxide dismutase	
Atrial natriuretic factor	
Erythropoietin	
Protein C	
Factor VIII	
Tissue plasminogen activator	
Industrial enzymes	

Note: These market projections encompass a range of technologies for producing products; cell culture is not the exclusive means of manufacture.

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TABLE 3. Mammalian Cell Culture Products and Indications

Product	Disease/condition
Lymphokines	Viral infections
Erythropoietin	Anemia, hemodialysis
Recombinant insulin	Diabetics, insulin dependent
Beta cells	Diabetics
Urokinase	Blood clots
Granulocyte stimulating factor	Wounds, severe
Tissue plasminogen activator	Heart attacks, survive to hospital
Transfer factor	Multiple sclerosis
Protein C	Hip surgery, protein C deficiency
Epidermal growth factor	Burns
Factor VIII	Hemophilia
Human growth hormone	Pituitary deficiency
Orthoclone	Kidney transplant rejection
Alpha interferon	Hairy-cell leukemia

TABLE 5. Companies and Organizations Involved in Mammalian Cell Culture and Related Activities, Worldwide

Country	No. of Companies	No. of Other Orgs.	Total
United States	453	126	579
Japan	83	17	100
United Kingdom	67	30	97
France	26	17	43
W. Germany	15	22	37
Canada	15	8	23
Switzerland	14	9	23
Sweden	14	2	16
Australia	13	1	14
Israel	10	4	14
Netherlands	9	2	11
Italy	6	11	17
Belgium	5	2	7
Finland	5	2	7
Austria	4	3	7
Denmark	4	2	6
South Korea	3	—	3
Singapore	2	—	2
China (People's Rep.)	1	2	3
India	1	1	2
Spain	1	1	2
Taiwan	1	1	2
Hungary	1	1	2
Argentina	1	—	1
Greece	1	—	1
U.S.S.R.	—	2	2
Cuba	—	2	2
Brazil	—	1	1
Mexico	—	1	1
New Zealand	—	1	1
Yugoslavia	—	1	1
Total	755	272	1027

tions are being developed by at least 145 companies. The economic losses attributed to animal diseases are estimated to be \$100 billion worldwide; many of the new vaccines should easily garner multi-billion-dollar markets. In a number of ways, development of vaccines for veterinary applications is ahead of human vaccine development.

Human vaccine market sizes are no less dramatic. The largest single vaccine market in the U.S. is for influenza, which, due to the emergence of different viral strains, requires repeated inoculations. Influenza is of

greatest concern for elderly people; as the general U.S. population ages over the next decade, more vaccine will be required. The new herpes vaccine will also achieve widespread application in the next five years. In addition, there will be substantial one-time markets for many new vaccines.

Mammalian cell culture can also be used to produce hormones, enzymes, and proteins. These products will have a profound impact on the way medicine is practiced, revolutionizing treatment methods. Examples of mammalian cell culture products and

TABLE 4. Numbers of Companies that are Involved in Products that can be made by Mammalian Cell Culture

Product	No. of Companies
Hepatitis B Vaccine	30
AIDS Vaccine	24
Human Growth Hormone	10
Erythropoietin	10
Superoxide Dismutase	6
Factor VIII	18
Protein C	2
Tumor Necrosis Factor	20
Atrial Natriuretic Factor	7
Colony Stimulating Factors	21
Macrophage Activating Factors	10
Platelet-derived Growth Factors	8
Epidermal Growth Factors	13
Kidney Plasminogen Activator	4
Tissue Plasminogen Activator	42
Interferons	53
Interleukins	54
AIDS Diagnostics	41

conditions they may be used to treat are shown in Table 3.

The world market for the six major human hormones and growth factors—insulin, growth hormone, fertility hormone, erythropoietin, epidermal growth factor, and estrogen—should reach \$1.9 billion by 1991. The human hormones insulin and growth hormone are already on the market; erythropoietin will soon follow. Animal growth hormones (referred to as somatotropins) enhance an animal's ability to utilize nutrients; somatotropins speed growth and, in the case of dairy cows, stimulate milk production. The world market potential for animal hormones will exceed \$2.5 billion by 1991; however, developing this market will depend substantially on regulatory agency approval. At present, there is considerable opposition from political lobbying groups. Farmers and other groups allied with farmers are trying to protect existing businesses.

Markets for interleukin-2, interferons, and other lymphokines should develop rapidly for the next several years as they are adapted for use in cancer therapies.

Perhaps the largest market for a cell culture product is for tissue plasminogen activator (t-PA). Presently in clinical trials, t-PA is extremely effective in dissolving several forms of blood clots. Although the demand for t-PA will increase rapidly between

1991 and 1996, competition will force its price down simultaneously.

The number of companies involved in producing each of 18 specific mammalian cell culture-derived products is shown in Table 4. In a more general sense, Table 5 sums the companies and institutions that work in cell culture and cell culture-related areas, worldwide.

Products FOR Cell Culture Technology

The markets for products used in mammalian cell culture production, while much smaller than markets for products produced by cell culture, are, of course, important to the biotechnology industry. For many of the companies that produce bioreactors, media, and other products used in cell culture processes, the next few years will provide great opportunities.

Although a number of different types of bioreactors are utilized in laboratory applications, hollow-fiber, airlift, stirred-tank, and fluidized-bed methods are used most frequently in mammalian cell production applications.

Because mammalian cell culture imposes some stringent require-

TABLE 6. Numbers of Companies Producing Media and Related Products

Type of Product	No. of Companies
Serum	14
Serum-free media	16
Unspecified media*	28
Extenders or supplements	11
Cell growth factors	11
Other related products	9

*Companies producing "cell culture media" the type of which is either unknown or does not fit into any of the other categories.

ments, especially in addressing the problem of cell fragility, some companies have specialized in contract production using their own bioreactors and methods to produce cells for end-users according to specification. Monoclonal antibodies represent the largest segment of the contract mammalian cell culture market.

A key ingredient in mammalian cell production is the medium in which the cells grow. The medium provides a source of elements, specific nutrients, and energy as well as removing heat and providing metabolic control.

Historically, fetal bovine serum has been used in mammalian cell growth

medium. Serum is a "natural" substance but contains a variety of components that can have negative effects on the efficacy of the final product. Serum is also extremely expensive. As a result, media have been developed that contain the essential components but omit those that have undesirable effects while attempting to optimize process economics. The media are supplied in various formulations, including serum-free media and media that contain both serum and additives.

To enhance the media according to the requirements of the particular product, a variety of extenders and supplements have been made available. In addition, cell growth factors that improve the performance of the bioreaction can be added; these too are produced separately. The numbers of companies identified as providing products in these areas are listed in Table 6. █

This article is based on Technology Management Group's recent market report, "Mammalian Cell Culture: A Worldwide Study on Markets, Products, and Technologies."

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