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GMP and Validation in Biotechnology

EDITORIAL

Technologies, Markets, and Regulations

Biotechnology has been rightfully recognized as one of the key technologies of the future, which will replace some of today's products and manufacturing procedures. It is mainly the therapeutic area which has, and will be, most affected by modern biotechnology. One can identify two specific groups of therapeutic agents, where biotechnology will play an ever increasing role in the production of pharmaceuticals:

a) the manufacturing of proteins and peptides
b) the manufacturing of optically pure drugs.

Technologies: Innovative Manufacturing Procedures and New Drugs

New or modern biotechnology came up with a number of innovative manufacturing procedures, which gave access to new categories of drugs. The most important innovation in modern biotechnology, besides hybridoma technology for the production of monoclonal antibodies, is the possibility of genetic recombination '*in vitro*'. Today's new drugs are increasingly manufactured using recombinant bacteria, yeasts, insect and mammalian cell lines. Human proteins (*e.g.* alpha-1-antitrypsin against emphysema) can be produced even by animal farming using transgenic mammals. It is evident that these specific manufacturing technologies also require specific validation and registration procedures.

Experience with proteins and fine chemicals has taught us, that for a validated manufacturing process meeting stringent product specifications, the decisive step is the isolation and purification of the product after fermentation or biotransformation. Generally the costs for down stream processing represent the major portion of the manufacturing costs. However, the simplicity of the product isolation and purification process is exclusively dependent upon fermentation (raw materials, biocatalysts, and procedures). The ideal result of fermentation and biotransformation is a cell free, aqueous product solution, virtually free of impurities and pyrogens. For these reasons also regulatory and validation aspects with respect to fermentation ought to be well planned.

Today, computers are integrally used in process control, product control, and inventory tracking. There is no doubt, that the future will see more and more computerized manufacturing systems also with fermentative processes. Standards of system validation and testing of these tools are consequently important. However, it should also be evaluated, to what extend on-line control during fermentation can be better used as quality control tool.

Markets: Recombinant and Optically Pure Drugs Will Command Large Market Shares in the Future

The elaboration of appropriate validation and registration procedures is important, since the global market potential and expected growth of the above mentioned products is considerable. The expected market value of proteins and peptides in the middle of this decade will be *ca.* 5 Bio $. One can expect that five to eight new proteins or peptides will eventually be available on the market every year, since over 150 new products are currently in clinical testing [1][2]. It can be anticipated, that of the 15 Bio $ market of new recombinant drugs in the year 2000 [1], a large part of this turn-over will be generated by peptides and proteins.

There is also an increasing shift from racemic to optically pure drugs. One important reason for the increasing chiral drug purity standards is the fact, that biotechnology offers new biocatalyzed methods for the production. In 1992, 13

optically pure drugs were sold for 200 Mio $, with an expected annual growth of 29% [3]. If one adds the possible substitution of existing racemates by optically pure products, the combined sales will reach 1.5–2 Bio $ in the middle of this decade.

The sales of proteins, peptides and optically pure products together in 1995 already will represent *ca.* 5% of the worldwide pharma market (*ca.* 150 Bio $), with the prospect of strong growth.

Regulations: Fermentation According cGMP

Biotechnological manufacturing processes must of course comply with current GMP (Good Manufacturing Practice) and other related consumer protection and quality assurance measures. Since the isolation and purification procedures have been used for long time in pharmaceutical (synthetic and extractive) industry, validation and registration procedures are straightforward. However, fermentation using recombinant organisms are often considered new operating procedures, although the underlying manufacturing principals are exactly the same as *e.g.* for antibiotics, where extensive experience has been collected over 50 years of reliable and safe production. Nevertheless, there are many different agencies and rules in relation to quality and validation. For example:

- USA: The biotechnological manufacture, *e.g.* new drugs and biologics for humans is reviewed for safety and efficacy by federal agencies such as FDA, USDA, and EPA.
- Europe: In the European community new drugs are registered by an agency for pharma specialities (CPMP). Moreover, member countries of the organization for economic cooperation and development (OECD) have also their individual reviewing and registration authorities, like the IKS in Switzerland or MCA in the United Kingdom.

Besides these government bodies for revision and registration of new drugs and their manufacturing processes, there are also a number of quality and safety related aspects handled by other authorities. For example:

- the European Commitee for Standardization (CEN) is currently elaborating standards for biotechnology with respect to *e.g.* specific operating procedures (*e.g.* strain conservation), control and testing procedures (raw material, equipment), unit operations (fermentation and DSP), *etc.*
- the certification according to one or several ISO norms.
- Biosafety regulations, which are regulated by each country individually, and which mostly copy the US rules.

Scope of the Conference

As mentioned above, there are many different government bodies, regulations rules and normes emerging with respect to manufacture with new biotechnology. With many different organizations and national authorities involved in the regulation of products destined for global markets, there is the risk of confusion and overregulations. Thus the aim of the conference is to review the regulation and validation situation with special consideration of fermentation and biocatalysis, which will be more and more the manufacturing method of choice in the future. It is mainly from the practical point of view, that the conference will address strength and weakness of the present regulatory situation. It is particularly important to review fermentation processes, since the simplicity, cost and ultimatively also registration and validation procedures for isolation and purification are exclusively dependent upon fermentation. The conference did concentrate on manufacturing processes using (submersed) fermentative processes, and did not consider production by transgenic animals.

[1] J. Drews, *Bio/Technology* **1993**, *11*, 16.
[2] E. Gwinner, *Chimia* **1994**, *48*, 89.
[3] D. Eardman, *Chem. Eng.* **1993**, October, 35.

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