Chapter 11

Proteomics for Development of Immunotherapies

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1. INTRODUCTION TO BIOPHARMACEUTICALS

Recombinant DNA technology has come of age. The first true application of this technology was the manufacture of therapeutic proteins. The first such biopharmaceutical product to come on the market was recombinant human insulin. This product, produced in *Escherichia coli* cells, was granted a marketing licence by the Food and Drug Administration (FDA) in October 1982. Until recently, all biopharmaceutical products were protein-based. However, since the 1990s, nucleic acid-based biopharmaceuticals have also come to prominence, being employed in gene therapy and anti-sense technology. The first anti-sense drug Vitravene®, for the treatment of cytomegalovirus retinitis in AIDS patients, was approved by the FDA in 1998. Today the definition of biopharmaceuticals refers to pharmaceutical preparations involving a protein produced by recombinant DNA technology or a nucleic acid-based compound as drug substance or active ingredient. Most notable among these biotechnology products are those for human therapeutic use, including hormones, growth factors, cytokines, monoclonal antibodies and vaccines. These products are used in a large number of therapeutic segments for the treatment of widespread pathologies, such as cancer, rheumatoid arthritis or asthma, as well as rare genetic disorders like Fabry or Gaucher diseases.

We will focus this chapter on therapeutic proteins, since their development, analytical characterization and commercialization are more advanced than that of nucleic acids.
1.1 The biopharmaceutical market

Since the beginning of the 1990s approvals of new biotechnology drugs and vaccines are rapidly increasing, with 22, 32 and 24 new biotech drug approvals and new indications for already approved drugs in 1999, 2000 and 2001, respectively. Biopharmaceuticals accounted for approximately 30% of all new molecular entities approved in the USA by the FDA in 2001 and 2002. In Europe, the situation is similar. Two hundred and sixty-five new pharmaceutical products have been granted marketing licences by the European Commission since 1995. Ninety-five of these were of biotechnology, representing 36% of all new drugs approved within this time-frame (Walsh, 2003). There are now more than 100 biopharmaceuticals already approved and available to patients in some world regions at least, with 88 having received approval within the European Union (Walsh, 2003). Among these 88 protein-based products, hormones and cytokines represent the largest categories, with 23 and 18 products respectively. Additional product categories include recombinant blood factors and related products, monoclonal antibodies and a range of subunit vaccines.

It is estimated that 250 million people have already benefited from medicines and vaccines developed through biotechnology, saving and improving their life. There are around 2000 biotechnology companies worldwide, and more than 180,000 employees working in this growing sector. Total biopharmaceuticals sales reached approximately 22 billion US Dollars in 2001, corresponding to 6% of the total pharmaceutical market, and are expected to reach 45-50 billion US Dollars by 2006. In 2001, the leading product category was constituted by erythropoietins, representing 26% of total sales. Immunotherapy products accounted for around 17% of total biopharmaceuticals sales, with 14% for monoclonal antibodies and 3% for vaccines. Other products accounting for significant market values were: interferons (16% of total sales), insulins (9% of total sales) and growth hormones (8% of total sales). Examples of a few highly successful biopharmaceuticals and vaccines are: Amgen’s erythropoietins for anemia and dialysis (‘Epogen®/aranesp’ 2001 sales: US$ 2.150 billion); Schering-Plough’s alpha interferon product for treating hepatitis C and various cancers (‘Intron®’ 2001 sales: US$ 1.447 billion); Eli Lilly’s product line for diabetics (‘Humulin®’ 2001 sales: US$ 1.061 billion) and GlaxoSmithKline’s hepatitis B vaccine (‘Engerix B®’ 2001 sales: US$ 750 million). Some antibody products launched in the past few years have almost reached blockbuster status, such as Johnson & Johnson/Schering Plough’s Remicade® for Crohn’s disease and rheumatoid arthritis, and Rituxan® for non-Hodgkin’s lymphoma from IDEC/Genentech, with sales of more than US$ 750 million in 2001.