

A suggested course detailing pharmaceutical biotechnology suitable for inclusion in undergraduate Pharmacy program in Iran

Pourahmad J., PhD

Assistant Professor, Dept. of Toxicology & Pharmacology, Faculty of Pharmacy, Shaheed Beheshti University of Medical Sciences

ABSTRACT

A 51 hour (3 credit) lecture course entitled pharmaceutical biotechnology is outlined which details the biochemistry and biotechnology of biological drug products. It is designed to equip students undertaking Pharmacy program with an understanding of concepts, both academic and applied, directly relevant to working in the biotechnological products sector. In addition to the course, a bank of relevant resource material is provided.

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Introduction

As far as we know the pharmaceutical industry is little more than half a century old. From modest beginnings it has grown rapidly. Today there are in excess of 10,000 pharmaceutical companies in existence producing about \$200 billion worth of product annually [1]. The development in the 1970s of the techniques of genetic engineering and hybridoma technology marked the birth of the modern biotech era. In terms of industrial application, these technologies exerted their most immediate effect on the healthcare sector, and led to the development of a new breed of pharmaceutical, the biopharmaceutical.

The first such substance to gain regulatory approval for medical use was recombinant human insulin (1982). The late 1980s and particularly the 1990s have witnessed the approval of some 50 such protein-based products in various world regions. By 1997 biotechnological products sales had reached \$7 billion, and is forecast to be in the region of \$35-\$40 billion by 2005, representing approximately 15% of the total pharmaceutical market [2]. Although all biotechnological products approved to date are protein-based, the advent of gene therapy and antisense technology will likely lead to the approval of several nucleic acid-based biotechnological products within the next decade.

Although exact figures are difficult to obtain, the biopharmaceutical industry represents a very significant employer of graduates whose primary degrees are exclusively/predominantly pharmacy-based. For this reason, and due to the cutting edge

nature of the science and technology underpinning this industry, it is desirable to include some details of the science/applications of these biomolecules in undergraduate pharmacy degree programs.

This paper outlines a suggested (51 hour lectures) course entitled Pharmaceutical biotechnology, suitable for inclusion in undergraduate Pharmacy program, which details the biochemistry and biotechnology of biotechnological products. The course as presented is best suited to courses in pharmacy.

It is designed to equip students with a basic knowledge of concepts directly relevant to working in the biopharmaceutical industry. The main areas of employment for biotechnologists/pharmacists within this sector are; Research and development, production, quality assurance and regulatory affairs. Issues relating to applied R&D are presented mainly in Section 2 of the course. Manufacturing issues are highlighted in Sections 3 and 5. Regulatory affairs are overviewed in Section 4 while QA issues form part of Section 5. Section 6 overviews a number of biotechnological products/product categories. In addition to familiarizing students with the biochemistry of the major biotechnological products, this section serves to illustrate how many of the generalized principles outlined in Sections 2-5 are applied in practice to specific products. There are some particularly useful sources of information underpinning this section (1, 3, 5) such as 'European public assessment reports' (EPARs), available via internet directly at

<http://www.eudra.org/humandocs/humans/epar.htm> or via EMEA home page.

Most previous experiments in teaching similar courses include a series of lectures detailing biological products. In the author's experience most such courses tend to focus upon the 'pure biochemistry' of such substances, while at best providing a superficial treatment of issues such as regulatory affairs or practical aspects of pharmaceutical manufacture. The course presented is designed to give equal prominence to such issues. As such it could be argued that it provides a more balanced comprehensive knowledge base needed by graduates to function most effectively when employed in the biotechnological products sector. For example, graduates working in R&D must have an understanding of manufacturing, regulatory and QA issues in order to develop a production process which can be adopted in practice for large scale production. Regulatory, quality and production issues are also intrinsically inter-linked in the manufacture of any pharmaceutical substance.

The course as presented may also be adapted in order to render it more suitable for Biochemistry/Applied chemistry M.Sc. programs. In addition to the course, a bank of resource material is provided, aimed at (a) assisting the lecturer preparing the course, and (b) assisting the students undertaking the course by providing additional reading material.

Course main aims

- a) To present a balanced overview of the biotechnological sector of pharmaceutical industry, emphasizing biotechnological products approved for general medical use.
- b) To provide an overview of important concepts as applied to the manufacture of parenteral pharmaceutical products, including biotechnological products.

Course specific objectives

- a) To impart an understanding of the terms 'traditional pharmaceutical product', 'biologic' and 'biotechnological products' (course outline, Section 1).
- b) To impart an appreciation of the drug development process and the regulatory roles played by the (US) FDA and the (EU) EMEA (course outline, Sections 2 and 4).

c) To impart a knowledge of the infrastructural details of a pharmaceutical plant manufacturing a parenteral product, and an appreciation of the principles of GMP as applied in such a plant (course outline, Section 5).

d) To provide an overview of the manufacture of a typical biotechnological product (course outline, Section 3)

e) To overview the biochemistry and biotechnology of a representative range of biotechnological products (course outline, Section 6).

Course outline

Section 1: Introduction (3 hours, 1 Lecture)

Overview of the pharmaceutical and biopharmaceutical industry; Definition of the terms 'traditional pharmaceutical product', 'biologic' and 'biotechnological product'; Advantages of producing biotechnological products by recombinant means (e.g. availability and scale of production, prevention of accidental transmission of disease, development of altered product forms via protein engineering); overview of biotechnological products now approved for use.

Section 2: Biotechnological drug development (9 hours, 3 lectures)

Overview of the drug development process; pre-clinical studies and clinical trials; Developing a recombinant therapeutic protein; Identification of potential biotechnological products, generation of suitable recombinant expression systems, characterization of the expressed protein, recombinant production in bacterial/animal cells; Plants and transgenic animals as potential sources of recombinant biotechnological products.

Section 3: The biotechnological products manufacturing process

(6 hours, 2 lectures)

Overview of cell banking systems ('master' and 'working'), and typical upstream & downstream processes; Fermentation, product recovery, concentration and chromatographic purification. Product stabilization and formulation into final product format (aqueous versus dry).

Section 4: Biotechnological product regulation (3 hours, 1 lecture)

Role of the regulatory authorities; organization and function of the (US) FDA and (EU) EMEA, with emphasis upon biotechnological product

regulation; The FDA's center for biologics evaluation and research (CBER), and the drug licensing process; The investigational new drug application, product license application (PLA) and establishment license application (ELA); The European medicines evaluation agency and its assessment of marketing license applications for biotech drugs; The rules governing medical products in the European Union; The international conferences on harmonization of drug regulations (ICH).

Section 5 Practical aspect of pharmaceutical manufacture (9 hours, 3 Lectures)

The pharmaceutical facility; clean rooms, cleaning decontamination and sanitation; Generation of water for pharmaceutical/ biotechnological products processing; Product flow through the facility and associated documentation; The QA function; Range and significance of biotechnological product impurities (micro-organisms, viruses, contaminant proteins, DNA, pyrogens); The range of QC tests carried out on typical biotechnological products; biotechnological product validation; Principles of validation, validation of chromatographic systems used in biotechnological product manufacture.

Section 6 The biochemistry, production and medical uses of selected biotechnological products (21 hours, 7 lectures)

Insulin; follicle stimulating hormone; Blood coagulation factors VIII and IX; erythropoietin; tissue plasminogen activator (tPA); the interferons; therapeutic/in vivo diagnostic applications of monoclonal antibodies; recombinant vaccines; gene therapy; basic approach, associated technical difficulties and target diseases.

Resource material

Books. The course may be taught entirely from the textbook 'Biopharmaceuticals; Biochemistry and biotechnology' [1]. Additional recommended reading (books) can include Ref [3-8] listed in the bibliography.

Useful internet sites. Particularly useful web sites include; <http://www.bio.org/> (*Biotechnology Industry Organization home page*), <http://www.phrma.org/> (*US pharmaceutical manufacturers home page*) <http://www.fda.gov/> (*US FDA home page*) and

http://www.eudra.org/en_home.htm (*EU EMEA home page*).

Articles. Research/review articles recommended to students as further reading will depend upon the relative emphasis the lecturer wishes to place on individual course topics, and the availability of specific journals. A comprehensive list of appropriate articles may be obtained from the bibliography of the books listed above. Relevant review/feature articles are most often published in journals such as Nature biotechnology, trends in biotechnology, current opinion in biotechnology, as well as annual reviews of biochemistry.

Videos. An excellent but expensive range of training videos detailing various practical aspects of working in a pharmaceutical plant are available from Micron Video International Ltd., Hampshire, UK (Tel. +44 (0) 1705 670 550; web page; <http://www.mvitraining.com/micron.video/>).

Discussion

The course described has been taught to the final year pharmacy students in University of Toronto since 1997. As a teaching assistant during my graduate studies in Faculty of Pharmacy, University of Toronto, I have been partly involved in teaching of the course for 3 years. Typically 15-20% of pharmacy students in University of Toronto subsequently gain employment in the pharmaceutical/biopharmaceutical industry (i.e.5-6 students from an average class of 30). Written student feedback collected each year upon completion (and marking) of the course (student anonymity preserved) clearly indicates that they feel the course contents and delivery fulfil the course aims and objectives. Oral feedback from a significant number of past students now employed in the biotechnological products sector echoes this. Consistently these past students cite the mix of academic and applicable knowledge as being the course's main strength. They cite the section detailing practical aspects of pharmaceutical manufacture as being particularly useful in performing well at initial job interview. These practical sections also helped the students to perform more efficiently in their new jobs, particularly over the first few months of employment.

Written student feedback illustrated that over 80% of students taking the course used the websites to source additional information, with more than 60% of students using the websites on a

regular basis (i.e. visiting it on 6 or more occasions).

The specific products/product categories listed in Section 6 of the course outline were selected on the basis of a number of criteria: (1) They represent an accurate overview of biotechnological products currently approved for medical use (course aims); (2) Many serve to illustrate specific concepts/points made in earlier sections of the course (e.g. overcoming problems of source availability or accidental disease transmission via recombinant production, generation of modified products via protein engineering); (3) Information relating to their biochemistry, medical applications and method of industrial manufacture is available in the literature (resource material section). Additional biotechnological products now approved for general medical use include human growth hormone, interleukin-2, and the therapeutic enzymes b-glucocerebrosidase and DNase. Although the market for such product is smaller than that of those cited in Section 6, and it is somewhat more difficult to source information detailing their industrial production, their inclusion in Section 6 would not be unreasonable. However, unless the course length can be increased, their consideration would necessitate the removal of some of the products currently included in this section.

Suggested course prerequisites would include basic biochemistry and molecular biology. A knowledge of basic microbiology and immunology would also be desirable (before undertaking this course, our students in Iran have gained a comprehensive grounding in biochemistry, microbiology, genetic engineering, immunology and chemistry with emphasis upon organic and analytical chemistry). In their final year relatively more emphasis is placed upon applied/industrial topics, with courses in industrial pharmacy (basic & advanced), good manufacturing practice, fermentation & bioprocess technology, bioinformatics as well as biological products being presented.

Although the course may be examined exclusively via written exams, inclusion of mini-projects should also be considered. Literature-based projects are most conveniently undertaken, with students being asked to research a specific biotechnological product, company, etc. The resource material, particularly the internet sites listed, should provide the information required by the students to undertake their mini project. The student may then prepare a written summary of his/her findings, and make an oral presentation

based upon these findings to the rest of the class. This can help improve the students' technical communication skills, skills which are also highly valued by employers in the (bio)pharmaceutical industry. (As delivered at University of Toronto the assessment strategy is based upon a written examination (80% of final mark), and a literature-based mini-project (8% of final marks for a written report and a further 12% for content, design and delivery of a 15 min power point-based oral presentation, and the ability to answer questions on the presentation).

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