

# REGULATION OF BIOPHARMACEUTICALS, TISSUE ENGINEERING AND BIOGENERICS: KEY ISSUES FOR THE DEVELOPER

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## **ABSTRACT**

The objective of the present study is to examine the effect of regulation on development of new biopharmaceuticals, tissue engineering and biologics. This includes defining key issues, which may influence the outcome of receiving marketing authorization. Most of the results are based on interviews conducted with experts with different backgrounds: regulators, representatives of biocompanies, investors, researchers and representatives of trade associations. Product information retrievable from the homepages of the EMEA and FDA has also been used as a data source. A review article is also included as it highlights central issues of the thesis and contains new information in addition to the review data.

Integration of regulation from the very early stages of product development and a sound understanding of regulatory requirements will have a positive impact on product development. However, detailed regulation is not necessarily available as new technologies push forth. This often leads to case-by-case evaluation, which is demanding and time consuming for both product developer and regulator. Tissue engineering is an example of such emerging technologies for which the regulation is still immature or lacking. According to the present study, a centralised evaluation seems the only possible route for ensuring uniform assessment of tissue engineering products. Currently product developers should develop products according to the medicinal products legislation, which also applies to biopharmaceuticals. Risk assessment and management is essential for Tissue engineering as the risks of these technologies are generally regarded as being substantial.

Biologics, called similar biological medicinal products in the EU legislation, are and have been in the focus of heated debate in the EU and USA although generics may be regarded as an inevitable step of the technological cycle. The pivotal regulatory issue is the question of comparability, for which the present study reflected no agreement. Control of post-translational modifications, immunogenicity and the extent of clinical trials required by the regulators pose major challenges for the biologics manufacturers. Thus, at the present time, biologics should be regulated on a case-by-case basis. Data from this thesis shows that intensified monitoring of the safety profile is called for. It is evident that risks of biotechnology-derived products are different from small chemical entities. This should lead to focused risk management programs. The main risk is the transmission of infectious agents. From the regulatory point of view, the risk management of biologicals is currently far from optimal as the appropriate

legislation lags behind.

The SPCs (Summary of Product Characteristics) of the EMEA and the PIs (Package Inserts) of the FDA of 32 approved biopharmaceuticals were compared. A general observation was that the EU SPC is more detailed in its instructions and the approach to safety information was clearly stricter. This difference may reflect the approaches to risk management of new medicinal products by the two agencies. Consequently, in spite of increasing harmonisation of the regulatory requirements, there are significant differences between the regulatory approaches that should be taken into consideration in drafting clinical development plans for biopharmaceuticals for global market.

# PREFACE

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Espoo, 14.3.2005

Outi Oila

## ORIGINAL PUBLICATIONS

This thesis is based on the following publications (Appendices I-V), which are referred to in the text by Roman numerals.

I Nieminen, O., Rahkamo, L. and Nordström, K., (2004) Biopharmaceuticals regulation in Finland: Challenges of the developer, regulator and investor. *Drug Information Journal* **38** 253-264.

II Nieminen, O., Kurki, P. and Nordström, K. (2004). Tissue Engineering, Viable Technologies Seeking for Regulation – A Finnish Perspective. *Drug Discovery Today* **9** (9) 387-391.

III Nieminen, O. and Kurki, P. (2004) Risk management of biologicals, *International Journal of Pharmaceutical Medicine* **18** (3) 149-157.

IV Nieminen, O. and Nordström, K. (2004) Regulation of Biogenerics, *BioDrugs* **18** (6) 399-406.

V Nieminen, O., Kurki, P. and Nordström, K., Differences in Product Information of Biopharmaceuticals in the EU and the USA: Implications for Product Development, *European Journal of Pharmaceutics and Biopharmaceutics*, in press.

### **The author's contribution in the appended publications**

I Outi Nieminen designed the research plan with co-authors. She was solely responsible for carrying out the experimental work and of the interpretation of the results. She has produced the manuscript with co-authors.

II Outi Nieminen designed the work with co-authors, carried out the experimental work and was responsible of the interpretation of the data. She has produced the manuscript with co-authors.

III Outi Nieminen designed and produced the review manuscript together with Pekka Kurki. Outi Nieminen was independently responsible for producing the majority of the sections addressed by the publication. Dr. Pekka Kurki added regulatory considerations.

IV Outi Nieminen designed and carried out the experimental work. Outi Nieminen produced the manuscript together with Katrina Nordström. Outi Nieminen was independently responsible for the focus areas of the study and the analysis of the data.

V Outi Nieminen together with Pekka Kurki designed the experimental part of the study. Outi Nieminen was responsible for the analysis of data and scientific interpretation of data with regulatory aspects covered by Pekka Kurki. The manuscript was produced with co-authors.

## ABBREVIATIONS

ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CHMP	The Committee for Medicinal Products for Human Use
COMP	The Committee for Orphan Medicinal Products
CPMP	The Committee for Proprietary Medicinal Products
CVM	Center for Veterinary Medicine
CVMP	The Committee for Veterinary Medicinal Products
EGA	European Generic Medicines Association
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ES	Embryonic stem cell
FDA	Food and Drug Administration
GAO	Government Accountability Office
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug Application
mAb	Monoclonal Antibody
NCTR	National Center for Toxicological Research
NIST	The U.S. National Institute of Standards and Technology
NDA	New Drug Application
OC	Office of the Commissioner
ORA	Office of Regulatory Affairs
PI	Package Insert
R & D	Research and development
RM	Risk Management
SPC	Summary of Product Characteristics
TGA	The Therapeutic Goods Administration
TE	Tissue engineering

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# 1 INTRODUCTION

## 1.1 BIOINDUSTRY IN THE EU AND THE USA

It has been estimated that annually an average of some 40 new pharmaceutical entities are developed of which about one quarter are based on the use of biotechnology<sup>1</sup> (Anon., 2004a). Biopharmaceuticals are currently available for the treatment of e.g. haemophilia, several cancers, diabetes, chronic hepatitis and Fabry disease. Several product groups of biopharmaceuticals have been approved in the European Union (EU). These include recombinant blood factors / blood related products, recombinant hormones, cytokines, vaccines, monoclonal antibody-based products and therapeutic enzymes and additional products (Walsh, 2003). Most of the biopharmaceuticals approved in the EU during 1995-1999 were recombinant proteins, which included e.g. several interferons and insulins. Another major product group was monoclonal antibodies (mAbs) (Reichert and Healy, 2001).

According to Walsh (2004), the majority of first generation biopharmaceuticals are unengineered murine monoclonal antibodies or simple replacement proteins displaying an identical amino acid sequence or alteration of the glycocomponent of a glycosylated protein. However, an increasing number of modern, second-generation products are being approved. Engineering to produce the second generation products may eg. entail alteration of glycocomponent or the covalent attachment of chemical moieties to an existing molecule. Reichert and Pavlou (2004) suggest that the likely commercial and research focus in the near future will be in two therapeutic categories of mAbs, namely those targeting oncology and arthritis, and immune and inflammatory disorders.

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<sup>1</sup> The term biotechnology and biotech is used in the present thesis to refer only to biopharmaceutical products, biomedical devices and companies within the biomedical field. Where reference is made to other areas of biotechnology a specific mention will be made.

In the USA, there are more than 1400 biotechnology companies, which employed almost 200 000 individuals at the end of 2003 (Anon., 2004b). However, although the number of biotech companies in the USA is smaller than in Europe, the US biotech industry employs twice the number of individuals in comparison to Europe. Consequently, there is a high employment growth potential in Europe. Economic growth of US biotechnology firms is strongly correlated to higher R & D (Research and Development) expenditures. In 2002, US biotech firms spent almost three times more on R & D than did their European counterparts (Anon, 2004c). Currently, the leading US biopharmaceutical companies are Amgen, Eli Lilly, Genzyme and Genentech. Examples of European companies are Novo Nordisk and Novartis (Table 1).

Table 1. Some of Biopharmaceutical companies and examples of their products (Walsh, 2004).

<b>Company</b>	<b>Product</b>	<b>Trade name of the product</b>
Centeon	rhFactor VIII	Bioclote
Genetix Institute	rhFactor IX	Benefix
Bayer	rhFactor VIII	Kogenate
Novo Nordisk	rhFactor VIIa	NovoSeven
Genentech	Alteplase	Activase
Boehringer-Mannheim	Retepase	Rapilysin
Eli Lilly	Insulin lispro	Humalog
Novo Nordisk	Insulin Aspart	Novolog
Aventis Pharmaceuticals	Insulin Glargine	Lantus
Genzyme	Thyrotrophin- $\alpha$	Thyrogen
Serono Laboratoires	rhGH	Serostim
Organon	Follitropin- $\beta$	Follistim
Amgen	rhEPO	Epogen
Schering Plough	rIFN- $\alpha$ -2b	Intron A
Hoffman-La-Roche	PEGinterferon $\alpha$ -2a	Pegasys
Merck	RHBaAg produced in <i>S. cerevisiae</i>	Recombivax

### **1.1.1 The bioindustry in Finland**

The bioindustry in Finland, including food biotechnology, environmental and pharmaceuticals, included 106 companies in 2001 with a total workforce of 1735 individuals. By far the largest sector (roughly 40%) is that of biopharmaceuticals and diagnostics development. The biocompanies, including also other areas than pharmaceuticals and diagnostics development, are located in few centralized areas, of which the Helsinki metropolitan area is the largest followed by the Turku region. Other major players are Oulu, Tampere and Kuopio (Luukkonen *et al.*, 2004).

The bioindustry as a whole is a fairly new business sector in Finland as 75 % of all biocompanies in Finland have been founded after 1990 (Luukkonen *et al.*, 2004). The use of biotechnology in the pharmaceutical industry has grown steadily over the past few decades also in Finland and Finland has been considered to be one of the leading countries in biotechnology in Europe (Anon, 2004d). Private and public investments in biotechnology research both in universities and biotechnology companies have been significant. Consequently, growth expectations for this area are high. Currently, with regards to the number of personnel, biopharmaceutical companies within Finland are large compared to small or medium-sized companies on average. The turnover of personnel is, however, smaller (Hermans, 2004). On the other hand as pointed out by Hermans and Ylä-Anttila (2004), it will take decades for biotechnology, as a separate sector, to reach the economic strength of the forest, electronics and metal industry in Finland, even if the growth of biotechnology would be strong. Regardless, biotechnology may have a significant role as a part of economic growth.

## **1.2 REGULATION**

### **1.2.1 The definition of a medicinal product, a biopharmaceutical and a medical device in the EU and the USA**

The terminology of many product categories within the pharmaceuticals and biomedical fields differs between the EU and the FDA. In the following the terminology<sup>2</sup> will briefly be introduced and references will be made to the appropriate documents defining these product categories.

#### **1.2.1.1 Medicinal product (EU) vs. drug (USA)**

Within the EU, directive 2004/27/EC (amending Directive 2001/83/EC) defines a medicinal product as "any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances, which may be used or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" (Anon., 2004e).

In the FDA, however, medicinal products are referred to as drugs, where the term drug is defined as "A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)" (Anon., 2004f).

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<sup>2</sup> The appropriate terminology adopted by the EMEA and the FDA will be used when addressing either one of these regulatory agencies. In more general areas the EMEA terminology will be used.

### **1.2.1.2 Biotechnological medicinal product (EU) vs. biological (USA)**

Biotechnological medicinal products in the EU are defined in Part A of Annex to Council Regulation (EEC) No 2309/93 (Anon., 1993a). Part A products are “products developed by means of one of the following biotechnological processes: r-DNA technology, controlled expression of genes encoding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, or hybridoma, and monoclonal antibody methods”. However, medicinal products produced by other biotechnological processes, which constitute a significant innovation, fall under part B.

The FDA does not have a formal definition for the term biopharmaceutical or biotechnological pharmaceutical. In the FDA, the term biological product refers to any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries to man (Anon., 2003b).

### **1.2.1.3 Medical device as defined in the EU and the USA**

In the EU the Council directive 93/42/EEC (Anon., 1993b) covers the definition and regulation of medical devices and accessories thereof. Accordingly, a medical device is defined as “any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of 1) diagnosis, prevention, monitoring, treatment or alleviation of disease, 2) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, 3) investigation, replacement or modification of the anatomy or of a physiological process, 4) control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means”.

In the FDA the term device refers to “an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the

official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (Anon., 2004 f).

### **1.3 REGULATORY AUTHORITIES AND MARKETING AUTHORIZATIONS**

#### **1.3.1 Stages of pharmaceutical development**

Biopharmaceuticals development in general follows the development protocols established by the pharmaceutical industry. The biopharmaceuticals, by inherent nature of the technologies and molecules, will however, set certain challenges for product development. Thus there is no standard route, by which the biotechnological products currently on the market have been developed. The steps of pharmaceuticals product development are briefly presented below.

Following the initial discovery of a potential medicinal product it will first undergo pre-clinical trials in animals. The particular aim of the pre-clinical trials is to establish the safety and efficacy of the potential new product. These studies include a range of pharmacokinetics and pharmacodynamics, toxicity studies, reproductive toxicity and teratogenicity, mutagenicity and carcinogenicity (Walsh, 2003). However, only a small number of medicinal products, including biopharmaceuticals that are tested in animals will ever reach testing in clinical trials. The product candidates that do pass pre-clinical trials will subsequently enter clinical trials, which are divided to three phases (I-III) with an additional post-authorisation phase, occasionally referred to as Phase IV. Phase I focuses mainly on safety. The aims of Phase I studies are largely to establish the pharmacological and the toxicological properties of the medicinal product in

humans and the appropriate route and frequency of administration of the medication for humans. Phase II focuses mainly on effectiveness and if the potential product proves to be safe and effective as established by the preceding studies, phase III trials are initiated. The very extensive phase III trials may include thousands of patients and are designed to establish the safety, efficacy and dosage (Shahala, Henney and Woodcock, 1999; Walsh, 2003). After completing trials successfully, the developer may proceed to apply for marketing authorization. Phase IV is a post-authorisation safety surveillance undertaken for some drugs that are administered over particularly long periods of time (Walsh, 2004).

### **1.3.2 The European Medicines Agency (EMA)**

The EMA is a decentralized regulatory agency of the European Union. The headquarters have been in London since January 1995. The main responsibility of the EMA is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The EMA works as a network, bringing together the scientific resources of the Member States to ensure the highest level of evaluation and supervision of medicines in Europe. The Agency cooperates closely with international partners on a wide range of regulatory issues. The scientific opinions of the Agency are prepared by three committees responsible for medicines for human use (CHMP), for veterinary medicines (CVMP) and for the designation of orphan medicines for rare diseases (COMP). The CHMP and CVMP consist of two members nominated by each Member State. The COMP has one representative of each Member State, together with three representatives each of patient groups and of the EMA. A network of over 3000 European experts underpins the scientific work of the EMA and its committees (Anon., 2004g).

A medicinal product within the jurisdiction of the EU must have a marketing authorization before it can be launched onto the market. Marketing authorization for a medicinal product can be applied for through the national procedure, a mutual recognition procedure, or the centralized procedure. The national procedure refers to the marketing authorization granted by Competent



authorities of member states, ie. national regulatory agencies. At present, the national procedure is mainly used in cases where marketing authorization is being applied for in one member state as the first country within the European Union. This procedure is also possible when the applicant applies for authorization for a new strength or pharmaceutical form. Under the mutual recognition, the applicant can choose a member state to be a reference member state. The member state, for which mutual recognition is sought, should recognize the marketing authorization granted by the reference member state, unless use of the medicinal product in question could present a risk to public health. However, for centralized assessment purposes, products will be evaluated by the EMEA and have to be classified in “part A”. All marketing authorizations of biopharmaceuticals have to be assessed via the centralized procedure. Granted authorizations are valid in all Member States (Anon., 2004h; Walsh and Murphy, 1999). According to Regulation (EC) No 726/2004, a centralised procedure should also be made compulsory for orphan medicinal products and any medicinal product for human use containing an entirely new active substance, i.e. one that has not yet been authorised in the Community, and for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder or diabetes (Anon., 2004i). Future medicinal products to be developed for targeting these therapy areas are expected to be biological products.

Within the EMEA, the Committee for Medicinal Products for Human Use (CHMP, formerly CPMP (Committee for Proprietary Medicinal Products)) performs the actual assessment of the application for medicinal products for human use. Every Member State nominates two scientific experts to the CHMP. The CHMP nominates a rapporteur and co-rapporteur to perform the assessment of each application, and the other members then comment on the rapporteurs’ assessment reports. Based on the assessments, the CHMP issues a scientific opinion within 210 days of the date of filing the application. The decision to grant marketing authorization is made by the EU Commission based on this opinion (Anon., 2004h).

### 1.3.3 The Food and Drug Administration (FDA)

Beginning as the Division of Chemistry and then (after July 1901) the Bureau of Chemistry, the modern era of the FDA dates to 1906 with the passage of the Federal Food and Drugs Act. Since 1930 the name of the FDA has been the present version (Anon., 2004j). The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation. The FDA consists of eight centers / offices, namely Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), Center for Food Safety and Applied Nutrition (CFSAN), Center for Veterinary Medicine (CVM), National Center for Toxicological Research (NCTR), Office of the Commissioner (OC), and Office of Regulatory Affairs (ORA) (Anon., 2004k).

The Center for Biologics Evaluation and Research (CBER) has, up to October 2003, been responsible for regulating biopharmaceuticals. However, certain product oversight responsibilities have since been transferred to the Center for Drug Evaluation and Research (CDER). Such products include monoclonal antibodies for *in-vivo* use, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of such products (except clotting factors) and other non-vaccine therapeutic immunotherapies. Under the new structure, the biologic products transferred to CDER will continue to be regulated as licensed biologics (Anon., 2004l).

Current Federal law in the USA requires that a drug must be taken through the marketing application procedure and be approved before it may be transported or distributed across state lines. It therefore follows that the sponsor must seek exemption from such a requirement if the product is to be shipped to many states to be used in clinical trials during the drug development and prior to formally

applying for marketing authorization. To do so, the sponsor must submit an Investigational New Drug application (IND) by which an exemption may be obtained from the FDA (Anon., 2004l). After clinical studies, the New Drug Application (NDA) application is filed. The NDA is the dossier, which drug sponsors must use to formally propose that the FDA approve a new pharmaceutical for sale and marketing in the USA. The data from preclinical studies on animals and human clinical trials of an IND are into the NDA (Anon., 2004n). After an NDA is received, the FDA is allowed 60 days to decide whether the NDA will be filed in order for it to be reviewed. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness. FDA reviewers will evaluate the drug and find it either "approvable" or "not approvable." (Meadows, 2002).

### **1.3.4 Biomedical products regulation in Japan, Canada and Australia**

The focus of the present thesis is on the EU and the USA. However, as international harmonisation will be addressed in this thesis, also the regulatory authorities of Japan, Canada and Australia are briefly presented.

In Japan The Pharmaceutical and Medical Safety Bureau under Ministry of Health, Labour and Welfare implements measures for securing the efficacy and safety of drugs/quasi-drugs, cosmetics and medical devices. This Bureau also implements safety measures for medical institutions and blood products, and measures against narcotics and stimulants. (Anon., 2004o).

Health Canada is responsible for regulating biotechnology-derived products under the Food and Drugs Act. These products include genetically modified (GM) and other "novel" foods; biologics, such as blood, blood products and vaccines, and genetics; assisted human reproductive technologies; and therapeutics such as drugs and medical devices (Anon., 2004p).

In Australia, The Therapeutic Goods Administration (TGA) is a unit of the

Department of Health and Ageing. The TGA carries out a range of assessment and monitoring activities and is responsible for ensuring that therapeutic goods available in Australia are of an acceptable standard. The aim is to ensure that the Australian community has access to therapeutic advances within a reasonable time (Anon., 2004q)

### **1.3.5 The International Conference on Harmonisation (ICH)**

Global development of new products faces many regulatory hurdles due to differences in legislation and regulatory environments across the national and international markets. Consequently, as of 1990, The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has been striving to bridge gaps between the regulatory authorities of Europe, Japan and the United States. Experts from the pharmaceutical industry have also been part of the ICH discussion on scientific and technical aspects of product registration. The goal of the ICH is to strive for a unified approach to recommendations for achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. These efforts are made in order to reduce or make redundant the need to duplicate the testing carried out during the research and development of new medicines (Anon., 2004r).

## **1.4 TISSUE ENGINEERING**

### **1.4.1 Definitions**

Tissue engineering represents a field of multidisciplinary collaboration between cellular and molecular biology on the one hand and materials, chemical and mechanical engineering on the other (Risbud, 2001). According to Fuchs *et al.* (2001) tissue engineering is a interdisciplinary field that applies the principles and methods of engineering and the life sciences toward the development of biological substitutes that can restore, maintain, or improve tissue function . Langer and Vacanti (1993) add that tissue engineering applies the principles of biology and engineering to the development of functional substitutes for

damaged tissue. Williams (2004) finds tissue engineering as a radically new concept for the treatment of disease and injury. It involves the use of the technologies of molecular and cell biology, combined with those of advanced materials science and processing, in order to produce tissue regeneration in situations where evolution has determined that adult humans no longer have innate powers of regeneration. On the other hand, according to Tabata (2001) tissue engineering is a newly emerging biomedical technique that involves the artificial manipulation of cells to promote tissue and organ regeneration. Tabata classifies tissue engineering into two main areas: tissue regeneration and organ substitution.

According to EU DG Enterprise consultation paper on proposal for a harmonized regulatory framework on human tissue engineered products (April 2004), a human tissue engineered product means any autologous (emanating from the patient himself) or allogeneic (coming from another human being) product which contains, consists of, or results in engineered human cells or tissues, and has properties for, or is presented as having properties for, the regeneration, repair or replacement of a human tissue or the new cells, where the new tissue or cells, in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaired or replaced (Anon., 2004s). In contrast, the FDA does not have a formal definition for the term tissue engineering. The U.S. National Institute of Standards and Technology (NIST) describes tissue engineering as: "Tissue engineering uses synthetic or naturally derived, engineered biomaterials to replace damaged or defective tissues, such as bone, skin, and even organs." (Anon., 2004t).

#### **1.4.2 Scientific background of tissue engineering**

The use of human-derived cells, tissues, or organs to help a patient is not new. Self-grafts, notably of skin, are common and generally well tolerated. Familial grafts are also well known. However, tolerance to living tissue from non-self will require a lifetime use of immunosuppressants. Conventional replacement and repair of tissues depends on the use of biocompatible materials, but the lack of

responsiveness to natural stimuli, e.g. growth factor stimuli, from the body limits their long-term usefulness. This explains the excitement about using cells with or without biomaterials as tissue engineering (Lloyd-Evans, 2004). The source of live cells may be either autologous (the patient's own donated cells), allogenic (same species or cells obtained from another human) or xenogeneic (cells of animal origin). Cellular therapies may be combined with noncellular components to create combination cellular/device products (Noguchi *et al.*, 2003). Three general strategies have been adopted for the creation of new tissue: 1) isolated cells or cell substitutes, 2) tissue-inducing substances and 3) cells based on or within matrices (Langer and Vacanti, 1993).

Use of tissue engineering has recently been studied in several different applications, such as in aortic heart valves (Zimmermann and Eschenhagen, 2003), bone tissue engineering and spinal fusion (Kruyt *et al.*, 2004), vascular, omental and nerve grafts (Herrick and Mutsaers, 2004), hepatic tissue engineering (Kulig and Vacanti, 2004), vascular tissue engineering (Nerem, 2004) and skin tissue engineering (El Ghalbzour *et al.*, 2004). According to Williams (2004) there are two types of tissues that are most commonly considered in tissue engineering products and processes: skin and cartilage.

The potential benefits of tissue engineering are very attractive. However, TE also entails several risks, which Williams (2004) has summarized as follows:

- Microbiological contamination associated with source materials, including the possibility of latent viruses, which may give to infectious diseases.
- Disease transmission, where some disease states such as cancer, blood disorders, and genetic conditions will have to be considered.
- Contamination associated with the production process
- The delivery of unwanted cells resulting in ineffective products
- The risk of mix-ups
- Risks associated with the modification of cells during the processes of cell amplification or differentiation
- Risks inherently associated with the scaffold and with as yet unknown cell-scaffold

interaction

- Risks associated with the achievement of sterility of the final product
- Risks associated with the potential toxicity of cryopreservatives, process additives and other residues as well as patient specific responses
- Risks associated with the performance of the final product

### **1.4.3 Emerging legislation for TE-products**

Tissue-engineering products do not fall within either the classical pharmaceutical or device regulatory systems today (Jefferys, 2003). Australia, the USA, and Canada are somewhat ahead of Japan in establishing a feasible regulatory approach. All four are currently ahead of the European Union (EU), but individual European countries and the EU as a whole are catching up. The issues faced by autologous tissue engineering and by allogeneic cell and tissue-derived products are rather different. Autologous therapies fulfill no such product definition that could be considered to be placed on the market in the classic sense as interpreted by EU legislation. Even greater challenges are faced by allogenic products (Lloyd-Evans, 2004). Currently, the only examples of commercialized allogenic products are skin replacements, such as Dermagraft (Anon., 2004u).

#### **1.4.3.1 Regulation of TE-products by the EMEA**

At the present time, there exists no specific EU-legislation covering the authorization of tissue engineered products. Existing regulations, specifically the Medical Devices Directive 93/42/EEC (Anon., 1993b) does not cover the therapeutic use of cells and tissues of human origin, nor does Directive 2001/83/EC (Anon., 2001), which regulates medicinal products for human use. This also largely holds true of Directive 2004/23/EC (Anon., 2004v), which lays down standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications. Where such manufactured products are covered by other directives, this Directive applies only

to donation, procurement and testing.

Consequently, in the absence of a specific regulation for TE – products, national authorities often authorize these products on a case-by-case basis. Such rulings will be based on existing EU rules on medical devices and medicinal products or on the application of other national rules, which may vary from one Member State to another. Consequently, the European Commission's proposal for Union-wide legislation will have to enter into a new legislative area offering also a more definite legislative framework for industry to work within. While the safety of new techniques must be ensured, it is important that the current regulatory dilemma does not deny the access of patients to innovative treatments (Anon., 2004w). One solution has been offered by the “Proposal for a Harmonised Regulatory Framework on Human Tissue Engineering Products” (Anon., 2004r), where the product is defined by a combination of product characteristics, pre-clinical and clinical testing specifications and the manufacturing process. This proposal presents a two-tiered approach, in which allogeneic products would be regulated by the centralised procedure and autologous products by the decentralised procedure.

#### **1.4.3.2 The FDA approach to tissue engineering products**

The Center for Biologics Evaluation and Research (CBER) currently regulates under 21 CFR Part 1270 human tissue intended for transplantation that is recovered, processed, stored, or distributed by methods that do not change tissue function or characteristics and that is not currently regulated as a human drug, biological product, or medical device. Human cells, tissues, and cellular and tissue-based products are regulated under 21 CFR 1271 (Anon., 2004x; Anon., 2004y). There are three essential rules on tissue engineering in the FDA: 1) “Human Cells, Tissues, and Cellular and Tissue-based Products; Establishment Registration and Listing”, 2) “Suitability Determination for Donors of Human Cellular and Tissue-Based Products” and 3) “Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-based Products; Inspection and Enforcement”.



The FDA is in the process of revising the regulation of human tissues, cells, and cellular and tissue-based products. The new regulatory approach would include a broader selection of products and more comprehensive requirements to prevent the transmission of communicable disease. Tiered requirements based on the characteristics of such products would become the basis of the new regulation (Anon., 2004x). Work has been ongoing on these aspects as of 1997 when the FDA published regulations and guidance documents needed to implement the "Proposed Approach to the Regulation of Cellular and Tissue-based Products". The steps that the FDA agreed to take in response to the recommendations made by GAO (Government Accountability Office) is included in the December 1997 report, "Human Tissue Banks: FDA Taking Steps to Improve Safety, but Some Concerns Remain" (Anon., 2004z).

#### **1.4.3.3 Business opportunities offered by TE – product development**

Tissue engineering has raised hype and hope for commercial success. However, the route to market has not been easy. More than 2600 full-time equivalents in 15 countries and 89 firms were engaged in tissue engineering research and development by the end of 2002 (Lysaght and Hazlehurst, 2004). Firms are active in several fields of tissue engineering (Figure 1). However, although e.g. the USA is considered to be the global leader in the commercialization of TE (Anon., 2003a) only four of twenty tissue-engineered products, which had entered FDA clinical trials were approved by 2004. The aggregated development costs exceed \$4,5 billion. Evidently, as stated by Lysaght and Hazlehurst (2004) tissue engineering is having difficulty transitioning from a development stage industry to one with a successful product portfolio, which is often the case for breakthrough medical technologies.

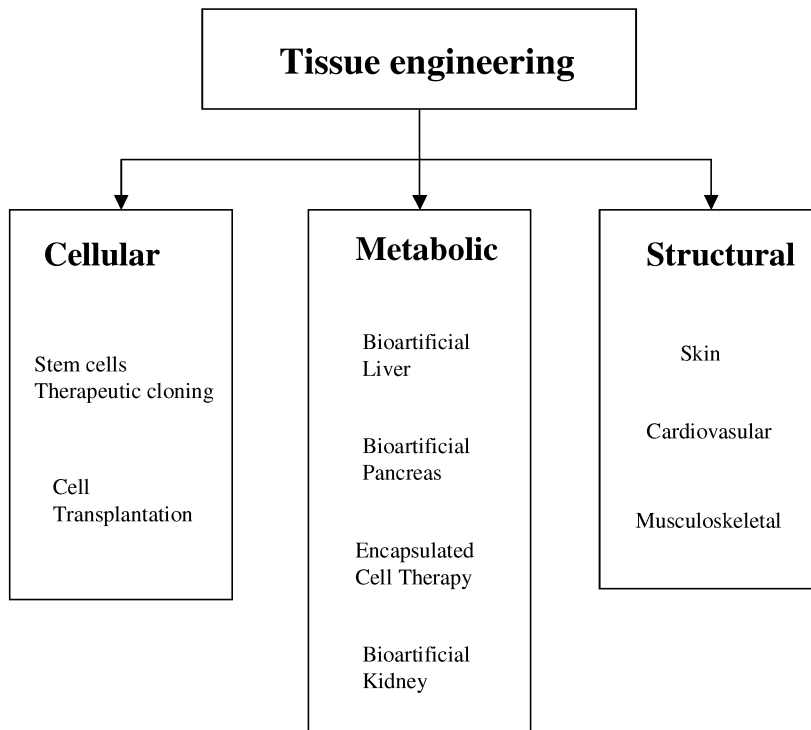


Figure 1. Areas with business activity (Lysaght and Hazlehurst, 2004).

## 1.5 BIOGENERICs: THREATS AND OPPORTUNITIES

### 1.5.1 Markets

As patents expire on biotech drugs, generic drug producers are investing heavily in the development of copycat versions of multi-billion-dollar medicines such as Intron A (interferon alpha 2b), Avonex (interferon beta 1a), Epogen (epoetin alpha), Procrit (epoetin alpha) and Neupogen (filgrastim) (Wysocki Jr, 2002, Firn and Simonian, 2004). Sales of the five major classes of biologics exceeded US \$22 billion in 2002 and it has been estimated that this may increase to US \$42.7 billion in 2007 (Griffiths, 2004). Biopharmaceuticals are usually expensive and savings are welcome for the health care sector. However, there are some hurdles to be overcome before biogenerics can be successfully marketed. Quality and safety cannot be compromised and one of the largest single uncertainty appears to be the global regulatory situation (Griffiths, 2004, Firn and Simonian, 2004). On

the other hand, competition by biogenerics is shunned by the innovative biotechnology industry, which hopes to see that the complexity of innovator products will make them immune to competition even as patents expire (Firn and Simonian, 2004).

Although the business of biogenerics appears to offer lucrative opportunities, biogenerics development is not an easy way to go for companies. A warning example of the perils and problems comes from Sandoz. Sandoz, the generics division of Novartis, developed its own version of the human growth hormone somatotropin, Omnitrop (Griffiths, 2004). Omnitrop received support from the CPMP in June 2003. However, the European Commission rejected Omnitrop and prevented it from becoming the first true biogeneric to be marketed in Europe (Winnick, 2004).

## **1.5.2 Why and how do biogenerics differ from other generics?**

Small molecules, such as aspirin, can be fully described in terms of their molecular structure. However, such characterization is not necessarily possible with biopharmaceuticals (Crommelin *et al.*, 2003). Biopharmaceuticals are (glyco)proteins, of which the building blocks form three-dimensional structures. Consequently, different areas in protein drug molecules may and will have different functions. A primary concern is the problem of immunogenicity in addition to the fact that the properties of biopharmaceuticals are dependent on many factors, including downstream processing and formulation (Schellekens, 2002).

### **1.5.2.1 Comparability is a central challenge**

Holovac (2004) is of the opinion that costly clinical trials that have established the safety and effectiveness of the innovator product, should not be required to be repeated in order for a generic drug to enter the marketplace. Once information has been established it would seem obsolete for the generics developer to re-prove the already previously proven safety and efficacy profile of the innovator product. However, this scenario of generic substitution is not as straightforward

as it appears with reference to the development of generic versions of biopharmaceuticals. Namely, the pivotal problem of bioequivalence is far more complicated for biopharmaceuticals than for small synthetic entities (Dove, 2001).

Change in the production process of a biopharmaceutical may cause change in physicochemical / biological characteristics, which for one may cause a change in the safety and efficacy profile (Dobbelaer, 2004). However, Chamberline (2004) is of the opinion that many products have an acceptably similar clinical efficacy and safety profile in spite of different manufacturing processes. These changes are a critical issue as it is well known that manufacturers of biotechnological / biological products frequently do make changes to manufacturing processes of products both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. The ICH Q5E provides direction regarding approaches to compare post-change product to pre-change product following manufacturing process and assess the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy. According to this guideline, the goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety and efficacy (Anon., 2004aa).

With reference to comparability, also immunogenicity becomes a central issue in the biogenerics debate. However, the causes of immunogenicity of biological products remain poorly understood. For example, even if the same genes are expressed in the same production hosts, and identical production methods are used, this does not necessarily lead to a similar degree of immunogenicity of the final protein product (Schellekens, 2002). Nonhuman protein sequences are also potent inducers of immune responses. In addition, protein aggregation may also induce immune responses as may also the creation of novel immunogenic epitopes through the formation of adducts with excipients and the presence of host proteins from bacterial or yeast derived products. As a solution to some of these issues Joneckis *et al.* (2003) propose that risk-based analysis should be used to

design the appropriate comparability incorporating also provisions for immunogenicity testing. In addition, Green *et al.* (2004) suggest that a comparability program should consist of the following key elements:

- biochemical characterization studies (structural identity)
- biological activity studies (potency and maintenance of mode of action)
- pharmacokinetic studies (dosimetry)
- toxicology studies (therapeutic ratio and safety profile)
- clinical trials (pharmacokinetics, pharmacodynamics, safety and efficacy)

### **1.5.3 EMEA regulation of biogenics**

The European Union has adopted the term similar biological medicinal products into the harmonised legislation. A marketing authorisation application of a similar biological medicinal product, as defined in Annex I of directive 2003/63/EC (amending Directive 2001/83/EC), must be supported by a complete quality documentation and data on comparable physicochemical and biological properties as well as on bioequivalence (Anon., 2003c). Furthermore, according to directive 2004/27/EC, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided (Anon., 2004e).

Within the EU, the similarity of two biologicals is demonstrated by a stepwise comparability exercise described in the Guideline on Comparability of Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality issues (Anon., 2003d). According to this guideline the three factors that should be taken into account in any comparability study are: i) the complexity of the molecular structure, ii) the type of change(s) introduced in the manufacturing process, and iii) their impact on quality, safety and efficacy. However, at the present time, only recombinant DNA and hybridoma products are within the scope of this guideline, and the guideline has not yet been used for the evaluation of similar biological products.

### **1.5.4 FDA regulation of biogenics**

For the US market, an abbreviated New Drug Application (ANDA) pathway, used for small molecule generic drug applications, does not presently exist for the majority of biologics, which are marketed under BLAs. However, as pointed out by Griffiths (2004) some biotechnological products have been approved under NDAs and therefore such drugs could be threatened by generic versions.

In the USA, the legislation covering generic substitutes draws on the Drug, Price Competition and Patent Restoration Act of 1984, commonly known as the "Hatch-Waxman Act". This is a federal law, which provides incentives to support the development of generic versions of off-patent drugs. The approval of generic versions of marketed drugs that are not exactly identical to the original product are allowed via a regulatory route known as a 505(b)(2) filing. The section 505(b)(2) pathway may also serve as a way to obtain regulatory approval of generic versions of certain biological products originally approved under a new drug application (NDA)(Anon., 1999). The section 505(b)(2) applicant must also provide any additional clinical data needed to demonstrate that differences between the original drug and its generic version have not changed the safety and efficacy profile of the product.

## **2 AIMS OF THE PRESENT STUDY**

The overall objective of the present study was to examine the effect of regulation on development of biopharmaceuticals and related new biomedical products and technologies. This involved pinpointing critical issues, which may influence the outcome of receiving marketing authorization. The specific aims were to:

1. Identify problematic issues of the regulation of biotechnological medicinal products and biogenerics thereof, medical devices and TE-products from the viewpoint of the developer, the regulator and to some extent the investor.
2. Examine the problematic regulatory issues identified as specified above and arrive at a conclusion as to the constraints imposed by these issues and present arguments to support possible solutions.
3. Compare the content of selected parts of marketing authorizations of biopharmaceutical products, which have been approved both by the FDA and the EMEA, in order to study the effect of differing regulatory environments on the final outcome of approval.

## 3 METHODS

The present study focuses on five major areas. The foundation was laid down by studying the regulation of biotechnological products (I) (Figure 2). The regulatory issues that were identified were then used to examine similar and emerging questions of the new tissue engineering (II) products in which the major regulatory challenge is the risk of biological products (III). As risk inherently ties also to comparability, biogenerics regulation was examined (IV). Finally, possible differences in the regulatory environment were examined by comparing the marketing authorization (V) of selected biopharmaceutical products in the EU and the USA.

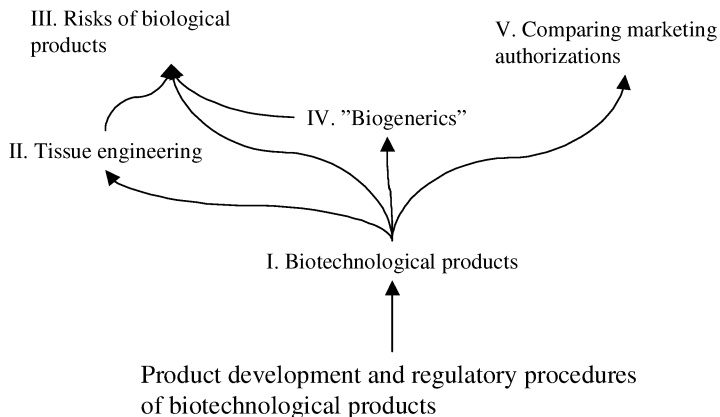


Figure 2. Focus areas of the present thesis.

### 3.1 INTERVIEWS

#### 3.1.1 Conducting interviews

According to Hirsjärvi *et al.* (2000) research interviews can be divided into structured (questionnaire), half structured (theme interview) and unstructured interviews. According to Mason (1996), the term qualitative interviewing is usually intended to refer to in-depth, semi-structured or loosely structured forms



of interviewing.

Altogether 88 theme interviews and 5 questionnaire studies were conducted. The theme interview is based on selected themes, where the questions within a theme complement each other and may be follow-ups of the answer given by the interviewee. The interviewer rather follows than leads the interviewee. In the theme interviews the interview does not proceed with detailed questions but, rather, key themes. This liberates the interviewer from the interview and emphasizes the role of the interviewee (Hirsjärvi and Hurme, 2000). Qualitative interviews are characterized by a relatively informal style, a thematic, topic-centered, biographical or narrative approach and by the assumption that data are generated via the interaction of the interviewer and interviewee (Mason, 1996).

Despite its relative flexibility, the theme interview is not without organization. The interview is guided by the interviewer and his or her agenda. The active interview guide is advisory, more of a conversational agenda than a procedural directive (Holstein and Gubrium, 1995). Mason (1996) would use rather term generating data than collecting data, when interview is a research method. According to Chirban (1996) essential aspects for interviewing are self-awareness, authenticity and attunement. The personal characteristics of the interview that one should recognize are integrity, motivation, trust, openness, empathy, insight, nurturance, truth, respect and faith.

Interviews of this study were conducted personally in place. These were conducted in the strictest confidence and did not involve the divulgence of any confidential information. The typical overall length of the interviews was approximately 1 hour. Questionnaires were chosen to be used in cases where personal interviews would have been unfeasible, due to scattered location of interview subjects in many different countries. The questionnaire study was essential in particular in publication IV, as at the time of the study, there were no biogeneric firms in Finland. Consequently, this was the only option for gathering information from companies abroad.

### **3.1.2 Research Population**

Expert interviews were used as a research method for publications I, II and IV. Data were collected during the years 2001-2003 by interviewing representatives of biotech companies as well as representatives of investors, insurance companies, regulatory authorities, research scientists and representatives of interest groups of pharmaceutical industry. According to Holstein and Gubrium (1995), individuals selected to interviews should be assumed to be capable of speaking reliably and validly for the population. Sampling is, however, an ongoing process as additional respondents might be added as newly emerging research interests or needs dictate.

In this thesis, the interviewees were carefully selected to be individuals, who would be expected to have a deep insight of the research area covered by the thesis. These were generally CEOs, product development directors, professors and senior regulatory authorities. Theme interviews were conducted both in Finland (at many locations around the country) and abroad (USA, UK, Belgium).

### **3.1.3 Limitations of interview as a research method**

Usability of theme interview as a research method should be evaluated by scientific criteria, where the most important requirement for scientific methodology is reliability. Factors contributing to reliability are concept validity, content validity, errors stemming from interviewers, choosing the interviewees and accuracy in transferring the information. Concept validity refers to the capability to reach essential features of the research object and it appears in defining the research problem and forming the framework for the interview. Content validity refers to capability of establishing themes and questions. Accuracy in transferring the information relates to transfer from tapes to written format (Hirsjärvi and Hurme, 1993). In the studies for this thesis, all these factors have been taken into account. It is, however, to be noted that in any interview individuals may also express self-serving biases. On the other hand, these may be less likely to be pronounced when the issues to be discussed are more abstract, (Babcock et al. 1995), as was the case in this thesis. Finally, the numbers of

individuals or case studies taking part or being the focus of any study will also set some constraints where the present thesis is no exemption. However, limitations, where appropriate, have been taken into account in the accompanying publications.

### **3.1.4 Data analysis**

Interview data was immediately encoded after the interview in order to avoid biased interpretation. However, as the data was in many respects qualitative, decisions had to be made at each stage as to the relevance of specific data and selection of such data for further analysis. Consequently, in order to proceed at an objective level when making such decisions, all interviewees were treated neutrally and therefore no distortion in interpretation of the data should have occurred.

One of the drawbacks that are associated with the type of qualitative data gathered in these studies, is the very large amount of text that is produced. In order to reduce the data and to find the critical issues to be compared the data was summarized by a minimum of two interpretative stages, where the text not pertaining to the question asked could be discarded. Quantitative data such as the percentage of respondents expressing a specific view was more straightforward to interpret. In many cases the interviewees were allowed to check their comments and accept them to be published. Notably, very few, if any changes were requested to be made, and the requests concerned rather minor editorial points than actual content.

### **3.1.5 Themes and questions**

Qualitative interviews require a great deal of planning and the structure and the flow of the interview must to be carefully outlined (Mason, 1996). In the present thesis, themes were set separately for each study. However, these themes were built around the information obtained by the previous study part and customized interviews were also made to find answers to specific research problems. In the

following the contents of the themes for publications I-V is introduced. Publication III will not be addressed in chronological order, as this is a review and will follow publication IV below.

### 3.1.5.1 Publication I

Publication I presents data on three main themes, namely 1) Products, 2) Product development, and 3) Regulation. As a modification to the interview method of Hirsjärvi and Hurme (2000), each theme consisted of 6-8 areas of focus. Selected focus areas are presented in table 2.

Table 2. Themes and contents of the publication I.

THEME	CONTENTS
Products	<ul style="list-style-type: none"> <li>• Drawing the line between biotechnological and conventional products</li> <li>• Drawing the line between medicinal product and medical device</li> <li>• Ethical questions</li> <li>• Product strategies</li> <li>• Problems</li> </ul>
Product Development	<ul style="list-style-type: none"> <li>• Most critical stages of product development</li> <li>• Problems</li> <li>• Financing</li> <li>• Critical factors for commercial success</li> </ul>
Regulation	<ul style="list-style-type: none"> <li>• Scientific advice</li> <li>• Orphan drugs</li> <li>• Taking marketing authorization procedure into account during the product development</li> <li>• Special problems of biopharmaceuticals</li> </ul>

### 3.1.5.2 Publication II

Publication II contained six themes: 1) awareness of regulation, 2) product development and regulation, 3) current regulation, 4) upcoming regulation, 5) risks and 6) future and finance. The interviews conducted for publication II were conducted with much more detail than in publication I. This was due to both the smaller number of experts available in Finland and also to more specific nature on

article. Selected focus areas are presented in table 3.

Table 3. Themes and contents of the publication II.

THEME	CONTENT
Awareness on regulation	<ul style="list-style-type: none"> <li>• Tissue engineering product groups</li> <li>• Regulatory awareness of developers</li> </ul>
Product development and regulation	<ul style="list-style-type: none"> <li>• Assessing regulatory issues: which regulatory issues are not taken sufficiently into account in early product development?</li> <li>• Identifying issues which can prevent products from entering markets</li> </ul>
Current regulation	<ul style="list-style-type: none"> <li>• Applying case-by-case evaluation</li> <li>• Legislation in the EMEA and the FDA</li> </ul>
Upcoming regulation	<ul style="list-style-type: none"> <li>• Changes needed to the legislation</li> <li>• EU wide vs. national regulation</li> </ul>
Risks	<ul style="list-style-type: none"> <li>• Risks of TE</li> <li>• Risks compared to medicinal products and medical devices</li> </ul>
Future and finance	<ul style="list-style-type: none"> <li>• Possibilities offered by TE</li> <li>• Strengths and weaknesses of TE in Finland</li> <li>• Financing the TE projects</li> </ul>

### 3.1.5.3 Publication IV

Publication IV is based on one hand on personal interviews and also on data obtained by an electronic questionnaire. The interviews contained four themes: 1) proving comparability, 2) legislation and regulatory procedures, 3) immunogenicity and 4) production and economics. This study gathered out by interviewing experts both in Finland and Belgium as the headquarters of the major organizations representing biogenerics (EGA) and innovator companies (EFPIA) are located in Brussels. Questionnaires sent to companies abroad served a central role. At the time of the study, “biogenerics” and their regulation were beginning to evolve and therefore formulating very specific questions in the absence of any preceding data was challenging. Thus questions were formulated in a manner which were specific enough to obtain a response but were also general enough to allow individuals with different levels of expertise to contribute to the study. Focus areas are presented in table 4.

Table 4. Themes and contents of the publication IV.

THEME	CONTENT
Comparability	<ul style="list-style-type: none"> <li>• Is it possible to address comparability?</li> <li>• Most demanding areas to prove comparability</li> </ul>
Legislation	<ul style="list-style-type: none"> <li>• What kind of regulatory procedure should biogenerics follow ?</li> <li>• Subgroups in legislation</li> <li>• Changes needed in legislation</li> <li>• Extensiveness of clinical trials</li> </ul>
Immunogenicity	<ul style="list-style-type: none"> <li>• Immunogenicity problems</li> <li>• Evaluation of immunogenicity</li> </ul>
Production and economics	<ul style="list-style-type: none"> <li>• Interesting products</li> <li>• Markets of biogenerics</li> <li>• Developing costs compared to innovative products</li> </ul>

### 3.2 PUBLICATION III – A REVIEW

Based on the perception that risk management is an essential part of biological products, risk management of different biologics was reviewed. The focus was on the European perspective but regulation of the FDA was also covered. Risk management of vaccines and blood products was chosen to present well-established risk management. rDNA and hybridoma, gene therapy and tissue engineering products highlighted the challenges of the risk management of biological and biotechnology-derived products.

### 3.3 PUBLICATION V - COMPARISON STUDY

The comparison study (V) was performed by comparing the SPCs (The Summary of Product Characteristics) of the EMEA to the PIs (Package Insert) of the FDA. A total of 32 marketing authorizations of biopharmaceuticals approved in the EMEA between 1995 and March 2004 were compared to the marketing authorizations of the FDA. The inclusion criteria for the products was that the product had to be a 1) biopharmaceutical or biological approved after the

founding of the EMEA in 1995 and 2) approved by both the EMEA and the FDA.

The SPCs and PIs are divided to several sections. The main emphasis of this study was on comparing 1) therapeutic indications, 2) contraindications, 3) content of warnings and precautions, 4) presentation of adverse reactions and 5) recommendations for the use during pregnancy and lactation. In addition 6) pharmacodynamics/clinical trials, 7) limitations to prescription, and 8) posology 9) paediatric prescribing and 10) preclinical information was examined. The date of approval and type of marketing authorisation and possible differences in supplied materials were also recorded as were also possible future investigations required by the authorities (commitments, special obligations). However, labelling and other necessary information was not available on the web pages of the FDA ([www.fda.gov](http://www.fda.gov)) for all products approved by the EMEA. Such products were excluded from this study. However, no product was otherwise intentionally excluded and thus the results are not biased. Furthermore, as all information could not be found for every product, identical issues could not be compared for every individual product. Overall, the majority of questions could be evaluated with reference to all products included in the study.

The study was mainly semiquantitative . This method was chosen as the information on many of the issues is expressed in very different format in the EMEA and the FDA. Consequently, numerical evaluation was not possible.

## **4 RESULTS AND DISCUSSION**

Publication I focuses on the identification of key issues in regulation of biotechnological products. Publication I is the first in the series of publications of this thesis and was conducted during 2000-2002. Publication I forms an umbrella under which data from publications II, III and IV will be discussed.

Publication II highlights many similar issues revealed by publication I that both regulators and developers face with the currently evolving TE products. Biogenerics (IV) is also an area where many of the most critical issues identified in publication I may be singled out for an examination of critical regulatory issues and allows also for solutions to the problems to be proposed. Publication III brings together studies in I, II and IV. The focus is on the inherent biological risks of the products, which the present thesis will present as one of the pivotal constraints of regulation. Where publications I-IV present data on other regulatory issues and aim to suggest possible solutions, publication V demonstrates that the regulatory environment may also influence the outcome of product development. Differences in approval of marketing authorizations in the EU and the USA are examined as a critical issue, which developers must anticipate, but may have little influence on.

### **4.1 IDENTIFICATION OF KEY REGULATORY ISSUES AFFECTING PRODUCT DEVELOPMENT (I, II, III, IV, V)**

Scale-up of manufacture, product purification, safety aspects and maintaining comparability with reference to possible changes in the manufacturing process, are key regulatory issues of production of biotechnological medicinal products (I). Scale-up and comparability were particularly relevant also for biogenerics (IV) and according to study III, it should be noted that safety aspects of biotechnologicals and biologicals are different from those of chemical entities.

According to the study I, the regulatory definition of product categories of new biotechnological products was a dilemma (fig. 3) as was also the case with TE products in (II). Similarly the terminology of biogenerics was not well-



established (IV). These findings demonstrate that common to new product development in these fields is the difficulty in categorizing products adequately.

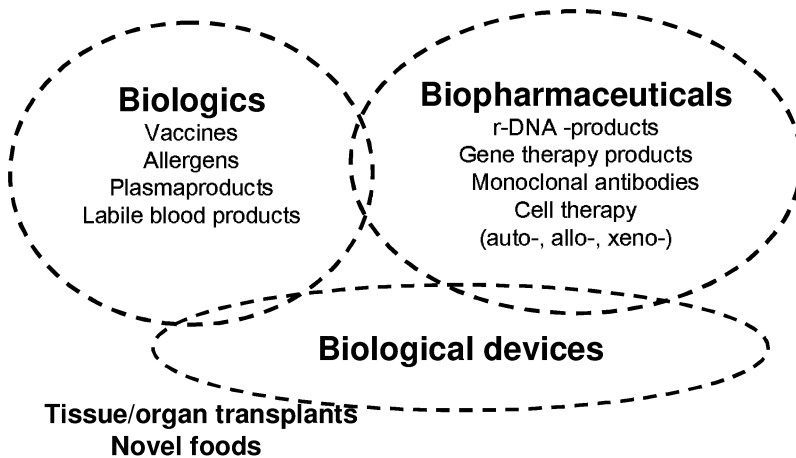


Figure 3. Drawing the line between product categories is difficult (Kurki, 2001 modified).

According to the results of publication I, integration of regulation of the appropriate product class from the very early stages of product development may be expected to have positive effects on the cost and timeframe of product development. However, it became evident that this is not always possible as regulation has not been available eg. for tissue engineering (II) and biogenerics (IV). In several of the studies conducted for this thesis (I, II and IV), it was evident that product developers expect regulation to be ready and waiting for products to be launched onto the markets. However, based on the studies for this thesis, the opposite should be anticipated. Product developers should be aware that in many cases products are initially evaluated case-by-case, when the technology is new and regulation is evolving (I, II, IV).

Biotechnological and related products are associated with many risks (both safety (III) and business risks (I, II, IV)), of which many stem from regulatory requirements. However, regulation can also be turned into opportunity and an asset. Having a good understanding of the regulatory requirements will assist the

developer and investor in identifying unviable projects at an early stage, thus reducing the risk of the loss of investments.

## **4.2 FUTURE CHALLENGES OF BIOTECHNOLOGICAL PRODUCTS**

Product developers, regulators and investors all expressed strong confidence in the growth and development of biotechnology in Finland at the time of the interviews, most of which took place in 2001. After that time the confidence in biotechnology was evidently lower as several biotechnology companies went out of business and did not live up to public expectations. However, Raunio (2004) is of the opinion that the confidence is being restored.

Most of the Finnish interviewees (I) believed that biopharmaceutical medicinal products will reach the public health care sector in Finland, but wider use in hospital outpatient care will depend on reimbursement. Biogenerics (IV) will clearly have an impact on prices of biopharmaceuticals. The question of how the expensive innovative products will find their place on the markets still remains. TE products (II) in particular may be expected to be fairly expensive, which may have an impact on their use. However, biotechnological and related products, such as TE products, will be an answer to several conditions, for which no treatments are available. Therefore even very expensive products will be justified to appear on the markets.

According publication I the orphan drug system was considered to offer a very good test base for developing new technologies. This may also in the future offer a possibility for focusing on the often rather simple heredity of the orphan disease, ensuring the product functionality, and broadening the area of indications of the product to a disease affecting larger populations. Acquired regulatory and commercial knowledge could also be used at a later stage e.g. for developing a blockbuster product.

As a solution to the declining number of biopharmaceuticals being granted marketing authorization, Pavlou and Reichert (2004) suggest new strategies

targeting shorter development times, higher success rates, innovative molecular engineering, robust intellectual protection and the development of cost-effective manufacturing. On the basis of publication I the present thesis suggests that such strategies for successful product development should include mastering regulatory affairs, anticipating product classification and clarification of reimbursement policies.

### **4.3 TISSUE ENGINEERING (I, II & III)**

The European Commission has announced plans to develop regulation for tissue engineering products . This future directive will create a new product class on the same level as medical devices and medicinal products. The main risks of cell-based and related therapies emerged as key issues in publication II and included transmission of infectious diseases, inflammation, carcinogenicity, risks related to immunity and risks involved with surgical procedures associated with the administration of the product. These findings are in accord with Heinonen (2003), Kleijwegt (2003) and Wassenaar *et al.* (2001) who have also concluded that the main risk of these products is the risk of transmission of infectious agents. Risks associated with TE according to Williams (2004) have been summarized in chapter 1.4.2. According to Williams (2004) the combination of risks contributes to the uncertainty that currently exists with respect to the commercial and clinical exploitation. Based on the literature review (III) the advanced therapies, gene- and cell therapies are areas where the risk assessment is not possible without the support of highly specialised experts in molecular and cell biology as well as virologists. Another special feature of the risk management of advanced therapies is the need for long-term follow up of patients.

Data from publication II demonstrated that defining tissue engineering was found to be difficult and a need for a sustainable definition for the legal basis of regulation was evident. The situation was thus akin to that seen in publication I, where new technologies push forth faster than a regulatory framework is available, and product classification emerges as a key issue. Clearly, the definition of a TE product should be based on scientific criteria that will make it possible to distinguish the TE products from medicinal products. Data from publications II

and III also demonstrate that at the present time, the existing legislation is not sufficient for covering all cell-based therapies and products and, for such products, there should be a new category and regulatory path. Also dividing TE products into subgroups were seen necessary for adequate assessment of the specific risks involved with certain technologies. A centralised evaluation seems to be the only way to a common approach to TE products that provides for the access to the common EU market.

Some reasonably simple products may be launched in the next few years, but according to publication II it will take 10-20 years until there are more sophisticated products on the market. It therefore follows that research groups that are currently in the concept stage of the commercialisation of cell-based product must recognize that regulation of new product classes evolves initially through a case-by-case evaluation (I and II) by the regulators. Legislative frameworks cannot be developed prior to the emergence of the scientific knowledge demonstrating the safety and efficacy of new products. Consequently, at the present time, for developers to bring TE products to the market, the most secure route is by observing and applying the most up-to date regulatory principles of medicinal products development.

Of the non-technological issues, ethical considerations are also key issues in TE product development (II) and are distinct to these products. Commercialisation of embryonic stem cells was seen as one of the major ethical problems even from a Northern European perspective. Adult stem cells were thought to be more likely candidates for TE, although their ability to differentiate was considered to be more limited. Consequently, ethical, rather than technological problems associated with ES (embryonic stem) cells appear to profile adult stem cells as more feasible candidates for TE product development. In addition to ethics, the major common non-technological denominator by the areas covered in publications I and II was availability of public and private funding. No differences were evident in either area (I or II), and both reflect similar problems in securing funding. However, the data available on funding from the studies for this thesis is not sufficient for drawing more detailed conclusions.

#### 4.4 RISKS (II & III)

Based on the literature review (III) it may be concluded that the risks of biotechnology-derived products and other biologicals are different from the risks of small chemical entities and, thus, their risk management will have special features. For many biological products, the safety is mainly dependent on the starting materials and the manufacturing process. Therefore, risk management must be focused accordingly.

Risk management of vaccines and blood products is well-established. The risk management of vaccines is influenced by the fact that the risks of the vaccines must be balanced with prospective benefits to the population rather than to immediate benefits of the individual him/herself (Anderson *et al.*, 1997). A risk-benefit consideration and a risk-based tiered regulatory framework may be partly suitable for the heterogenous groups of TE products (II). Testing of donors with state of the art assays is essential in the management of known pathogenic agents for blood products (III), and will be a necessity also for certain TE products. Furthermore, as for blood products (III), the risk of window donations and unknown agents must be taken into account when the manufacturing process is designed for TE-products (II). The handling of the risk of transmission of prions has been one of the most difficult tasks of the regulators and the companies (Guertler, 2002; Hoots *et al.*, 2001).

In conclusion, risk is a key issue in the regulation of TE and similar products, which involve the use of living cells. Consequently, developers should anticipate participating in the development of adequate risk management protocols, as the scientific novelty of new products cannot be assessed without close cooperation between academics, industry and regulators. In addition, some biological products are associated with serious public health risk and may even require efforts for establishing risk management protocols at the global level.

## 4.5 BIOGENERICS (IV & III)

According to publication IV biogenerics should be regulated on a case-by-case basis. These products present a diverse group of possible product alternatives. The data in publication IV shows that interviewees were not unanimous as to whether comparability can be addressed and what are the most challenging areas for proving comparability. Immunogenicity was considered to be a major problem for biogenerics as an immune response can lead to changes in efficacy and safety. Therefore, a requirement for an intensified monitoring of the safety profile during post-authorisation was thought to be justified in many cases (IV). Also based on the literature review in publication III a post-authorisation risk management programme will be required, especially to monitor the immunogenicity of the similar biological product (Loüet, 2003). A proper risk management program for immunogenicity is based on a set of adequate assays and on the data obtained during the pre-authorisation studies of the potential impact of the antibodies. From the generics company point of view, the risk management of biogenerics is more demanding than the risk management of conventional generics.

Biogenerics may be used to illustrate in more detail some key regulatory constraints (Figure 4). Possible solutions for such constraints may also be suggested. In publication IV, the competitiveness of biogenerics was the basis for the analysis in Figure 4, where it was proposed that the solution to the most challenging issues may lie in mastering demanding technologies. These would need to have a clear regulatory status. On the other hand, it is evident that these technologies are clearly the current prime competencies of the innovator. Consequently, it may be suggested that biogenerics developers may be wise to focus on acquiring skills associated with less demanding, technologically feasible and regulatory approvable solutions.

On the other hand, by examining the conclusions drawn for publications II and III above, it is evident that comparability is inherently tied to risk and is also reflected in Figure 4. The discussion in publication III thus concerns also biogenerics. The pharmacovigilance specification and risk management of rDNA and hybridoma products and any generic versions thereof will require a

multidisciplinary approach. Immunogenicity, as for innovator products is the main threat for the long-term efficacy and safety. Because the mode of action and the targets of recombinant proteins and hybridoma proteins are often well known, potential risks can often be predicted (III). However, the potential risks may be difficult to verify (III and IV). Risk management of gene therapy requires in depth understanding of molecular biology of the gene constructs and viral vectors as well as of their integration and/or influence on the desired and potential target cells (Anon., 2003e).

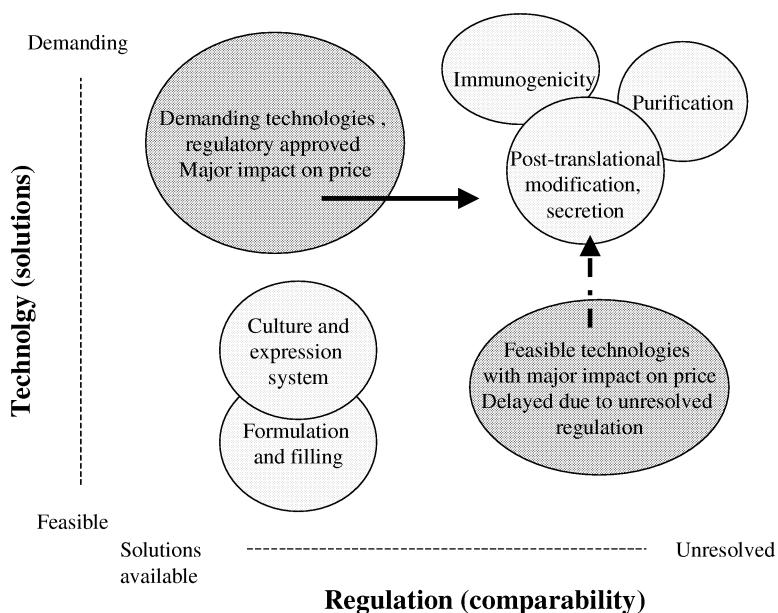


Figure 4. Some constraints of regulation and technologies on selected issues of product development in a hypothetical setting.

In conclusion, for biogenerics there is a need for a defined basic package of clinical studies and some data requirements can be added on this package. The extent of the data should be determined in part by considerations related to product quality, the disease to be treated, product-specific clinical pharmacology/toxicology issues and product-specific clinical trial design issues. Developers must also be prepared for a case-by-case regulatory evaluation.

## **4.6 COMPARISON OF MARKETING AUTHORIZATIONS (V & I)**

The examination of the EU SPC and the US PI, demonstrated that the differences between these documents for 32 selected products were not striking (V) (table 5). The number of therapeutic indications was usually the same in the EU and in the USA. However, the therapeutic indications granted in the EU were often significantly restricted as compared to the USA. The approach to safety information, notably to contraindications and warnings, was clearly stricter in the EU SPC. The contraindications of the EU SPC were often presented as warnings / relative contraindications in the US PI. In spite of this, the EU SPC often contained more warnings.

Instructions for use during pregnancy were not consistent between the continents as the EU SPCs imposed markedly stricter restrictions. The approach to lactation was also stricter in the EU SPCs as compared to US PIs. These differences may reflect the approaches to risk management of new medicinal products by the two regulatory agencies. The description of clinical trial data, including efficacy, in the US PI is very detailed. This may allow the prescriber the possibility to make his/her own judgement on the clinical efficacy.



Table 5. Comparison of indications, contraindications, warnings and precautions and adverse reactions of biopharmaceuticals in the EMEA and the FDA.

Indications			Contraindications, warnings & precautions and adverse reactions		
<b>Number of the indications</b>	Same	31	<b>Contraindications</b>	Equal number	12
	More in the EMEA	1		More in the EMEA	18
	Less in the EMEA	0		Less in the EMEA	2
<b>Number of restrictions for the use</b>	Same	17	<b>Warnings and precautions</b>	Equal number	15
	More in the EMEA	11		More in the EMEA	11
	Less in the EMEA	4		Less in the EMEA	6
<b>Specificity of wording</b>	Same	12	<b>Adverse reactions</b>	Similar presentation	14
	More detailed in the EMEA	8		More detailed in the EMEA	3
	Less detailed in the EMEA	12		Less detailed in the EMEA	15

A typical difference between the EMEA and FDA is the approach to positioning of the new biopharmaceuticals towards the existing treatment options in the EU. The EU regulators favour the use of active-controlled clinical studies in addition to the placebo-controlled studies. Differences between the EU and US are to be expected as the EMEA is co-ordinating a network of national experts in the EU whereas the FDA operates a fully centralised licensing system. Under these circumstances, compromises to settle divergent views may lead to a stricter approach that has an impact on product information in the EU SPC. However, the reasons for differences may have much deeper roots in the diversity of circumstances within the EU, including characteristics of the health care systems

and the legal frameworks and as well as cultural, moral and religious values of the societies.

A general observation was that the EU SPC is more detailed in its instructions to the prescriber. In contrast to the EU, the regulatory procedure in the US requires regular contacts to the FDA in order to ensure the compliance of the development program with the local regulations and the regulatory praxis. Therefore, the data from development programmes are tailored for the USA. It is to be expected that such a dossier will meet more questions when submitted to the EU. It is possible that the tendency of companies, revealed by studies for publication I, to send applications first to the FDA is a reflection of these differences in addition to the fact that the FDA development programs was perceived as being more supportive (I). However, according to study V, this may not be the only reason as also less restricted indications and fewer contraindications give wider markets to the biopharmaceutical.

The data in publication V does suggest that the regulatory environment in the EU is stricter than that of the USA. Product developers may need to be aware of such a trend, although it must be kept in mind that study V did have certain limitations with reference to the number of products studied and the data included from the SPC and the PI from each product.

## 5 CONCLUSIONS

Studies of the present thesis were undertaken to pinpoint regulatory requirements of biotechnological product development. Possible solutions to some of the problematic regulatory issues facing future product development were also addressed.

The most problematic issues of integrating regulation into product development stem from difficulties in defining product categories and the emergence of such products into an immature regulatory arena (I-IV). This will inevitably lead to case-by-case assessment by the regulatory authorities, the outcome of which may be difficult for the developer to proactively anticipate. Consequently, developers should become increasingly aware of regulation, seek regulatory and scientific advice and follow established regulatory demands. Although not a regulatory issue, developers should also be aware of reimbursement principles during product development.

Biological material is inherently tied to several distinct risks that must be evaluated and controlled. These risks differ between the product groups and consequently legislation and product development should be planned accordingly. In the case of TE products, the forthcoming regulation may be expected to be at least as stringent as that of medicinal products. Developers should be prepared for the need for long-term follow-up of advanced therapies, which adds additional responsibilities to the developer. Biogenerics developers should similarly prepare for an intensified monitoring of the safety profile during post-authorisation where immunogenicity is a primary concern. Changing manufacturing technologies will raise the issue of comparability, which may not have been previously addressed. Biogenerics development also raises the question as to whether biopharmaceuticals development as a whole will benefit or suffer from the expansion of the business sector. An essential point in such a discussion is also how a balance can be found between the business of biotechnology and the needs of public health care.

The present thesis is the first to show evidence for differences in the marketing authorisations issued by the FDA and the EMEA for biotechnologicals. SPCs and PIs showed differences indicating that the EMEA is prone to use a strict labeling and limited prescription. In view of the different approaches of the EMEA and the FDA, developers should pay attention to designing clinical development programs according to requirements of each respective agency.

Regulation sets strict requirements on quality, safety and efficacy. Meeting these requirements is very challenging especially for small companies. However, based on the results of this thesis, regulation as such is not a negative issue, but on contrary strengthens consumer/patient protection. There are past examples of serious consequences due to lack of such protection, e.g. HIV, hepatitis B and C, where insufficient regulatory alert lead to inadvertent contamination of biological products. A strict regulation can also increase public confidence and reduce populist opposition.

Regulatory knowledge also offers a competitive advantage to product developers. Results will be obtained faster, when the need to possibly repeat studies is made redundant. Proper and usable regulatory documentation will also fetch a more competitive price when licensing a product. Regulation may also be turned into a competitive asset at the international level.

The regulation of biotechnological products and similar products thereof is currently evolving and the existing regulation of the EU and the US still calls for harmonisation. Harmonisation would be a necessary tool for offering solutions to regulatory constraints also identified in the present thesis. Harmonisation is critical, not only for the developer and the regulator, but primarily for making new, safe and effective products accessible to patients.

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