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Research paper

Manufacturing, regulatory and commercial challenges of biopharmaceuticals production: a Finnish perspective

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Abstract

Biopharmaceuticals product development is a broad and multidisciplinary field. Science and technology are combined with new manufacturing, regulatory and commercial challenges. However, although there is ample literature on the molecular biology and biochemistry of products, the implementation of processes from test tube to commercial scale has not received similar attention. Consequently, the present study aims to highlight, from practical point of view, some of the key issues involved with manufacturing technologies of biopharmaceuticals at a commercial scale. Regulatory requirements and investments are also addressed based on the practical experiences of start-up and small companies. Finland is used as a case-example of such companies as this is a EU-member state with strong technological growth and rapidly increasing number of biotech companies.

Keywords: Biopharmaceuticals; Biotech engineering; Manufacturing; FDA/EMEA regulations; Scale-up; GMP

1. Introduction

The market share of biopharmaceuticals is rapidly increasing. It has been estimated that there are currently some 1000 new biopharmaceutical products in the development pipeline globally, of which some 400 are already in Phase II/III Clinical Trials [1]. Numerous biopharmaceuticals are also already on the market. By 2003 the European Agency for Evaluation of Medicines (EMEA) had approved 88 [2] and the Food and Drug Administration (FDA) 95 biopharmaceuticals [3]. It has also been estimated that more than 40 new biopharmaceuticals will be approved each year over the next 5 years [4]. The growth of the market for biopharmaceuticals is also driving a need for increased manufacturing capacity, which has been estimated to double by 2006 [5]. However, as production of sterile medicinal products such as biopharmaceuticals requires facilities with contamination control and clean room technology [6] the construction of new facilities is very expensive, ranging from $50 million for a small pilot plant to over $400 million for a commercial facility each. In addition, it takes over 4 years to bring new facilities on line, as all new manufacturing premises and processes have to be validated by regulatory authorities [7].

Regulatory authorities require that all biopharmaceutical products must be manufactured according to current Good Manufacturing Practice (cGMP) guidelines [8]. Accordingly, products must be manufactured in a reproducible and documented manner to guarantee the highest possible quality, safety and efficacy of the product [9]. Manufacturing premises and equipment have to be located, designed, constructed, adapted and maintained to suit their intended operations. Their layout, design and operation should minimize the risk of errors and permit effective cleaning and maintenance [10]. Any changes in fermentation, extraction, purification and formulation procedures may alter the properties of the final product. Process modifications, e.g. during scale-up are allowed only if the manufacturer can show that the final product of the modified process is comparable to the initial product. In addition,

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the biological activity and quality specifications of the product must remain the same. Large and complex biomolecules such as proteins are especially sensitive to these changes [11], which may lead to altered primary, secondary and tertiary structure and variations in post-translational modifications such as glycosylation [12]. The comparability of products is proven by showing that they are similar in terms of quality, safety and efficacy [13]. If the product manufactured by the modified process is not comparable to the original product, it will be considered as a new product and it has to be fully evaluated by regulatory authorities [14].

During the last 10 years a vibrant biotechnology community has developed and in 2003 there were more than 120 biotechnology companies in, e.g. Finland [15]. However, even though there is ample literature on the biochemistry, chemistry and molecular biology of biopharmaceuticals, the literature on the technical implementation, regulation and scale-up of biopharmaceuticals is scarce. Thus the aim of our study was to assess what types of technologies are needed for the manufacturing of biopharmaceuticals and the challenges companies developing biopharmaceuticals will be facing as they proceed to commercial scale production. Furthermore, a central challenge is to prepare for the regulatory requirements, which should be anticipated in the design of manufacturing capacity, processes and facilities.

2. Study design

The data for this study was mainly gathered by interviewing representatives of the Finnish pharmaceutical and bioindustry. Here, Finland is used as a case-example of a EU-member state with a strong technological background, but the data is applicable to biopharmaceuticals product development in general from the viewpoint of start-up companies. Companies were selected by gathering information from the homepages of pharmaceutical and biotech associations as well as science parks and technology centres (Table 1). Selected companies were approached via e-mail and personal interviews were conducted. Thirteen companies, including biopharmaceutical and biomaterial developers, contract manufacturing organizations and other service providers took part in interviews. The main topics of interviews were the products, manufacturing methods, manufacturing premises and staff. The interviewees' personal opinion on the future needs of the bioindustry was also a valuable contribution to the study. The limitation of the study is that as it covers the production process from laboratory through unit operations and scale-up, it cannot address all individual details. On the other hand, the study does attempt to highlight the most critical issues for proactive planning of production processes.

Table 1
Homepages of Finnish pharmaceutical and biotech associations and science parks and technology centres

Name	Homepage
Pharma Cluster Finland	http://www.pharmacluster.com
Finnish Bioindustries	http://www.finbio.net/home.htm
Pharma Industry Finland	http://www.pif.fi
Helsinki Business and Science Park Ltd	http://www.hbsp.net/
Technology Centre Teknia Ltd	http://www.teknia.fi
Medipolis Ltd	http://www.medipolis.com
Turku Science Park Ltd	http://www.turkusciencepark.com
Finn-Medi	http://www.finnmedi.fi/english/

Data obtained from public source.

3. Process development requires technological, engineering and regulatory skills

Process development is an integral part of biopharmaceuticals development. It is mainly driven by regulatory requirements for product quality and quality of the process (e.g. robustness, reproducibility). Properties of the end product guide the process development and process conditions must maintain product quality throughout the process. Process conditions must, e.g. ensure that the form and possible glycosylation of the product remains comparable from batch to batch.

3.1. Selecting, maintaining and cultivating host cells for production

Developers stressed the importance of the initial selection of a suitable cell line. Any change in the cell bank during clinical studies requires additional regulatory documentation and experimentation, which leads to increased costs and may delay the supply of material for ongoing clinical trials significantly. Special attention should be paid to the ability of the host cell to produce stabile molecules. In addition, a high rate of expression is desired to enable later up scaling of the manufacturing process. The initial selection of host cell also influences the design of the down stream process and the number of required unit operations (Fig. 1) that means 'scalability' is a critical issue. A well-known problem with recombinant eukaryotic proteins produced by prokaryotic microorganisms such as *Escherichia coli* is their tendency to accumulate inside the host cell and form insoluble inclusion bodies, which must be dissolved to release the protein [16]. In addition, proteins forming inclusion bodies are incorrectly folded and require additional chemical or enzymatic modifications to regain their native biologically active form, which also should alert the developer to prepare for increases the number of unit operations. In addition, the composition of the culture medium was

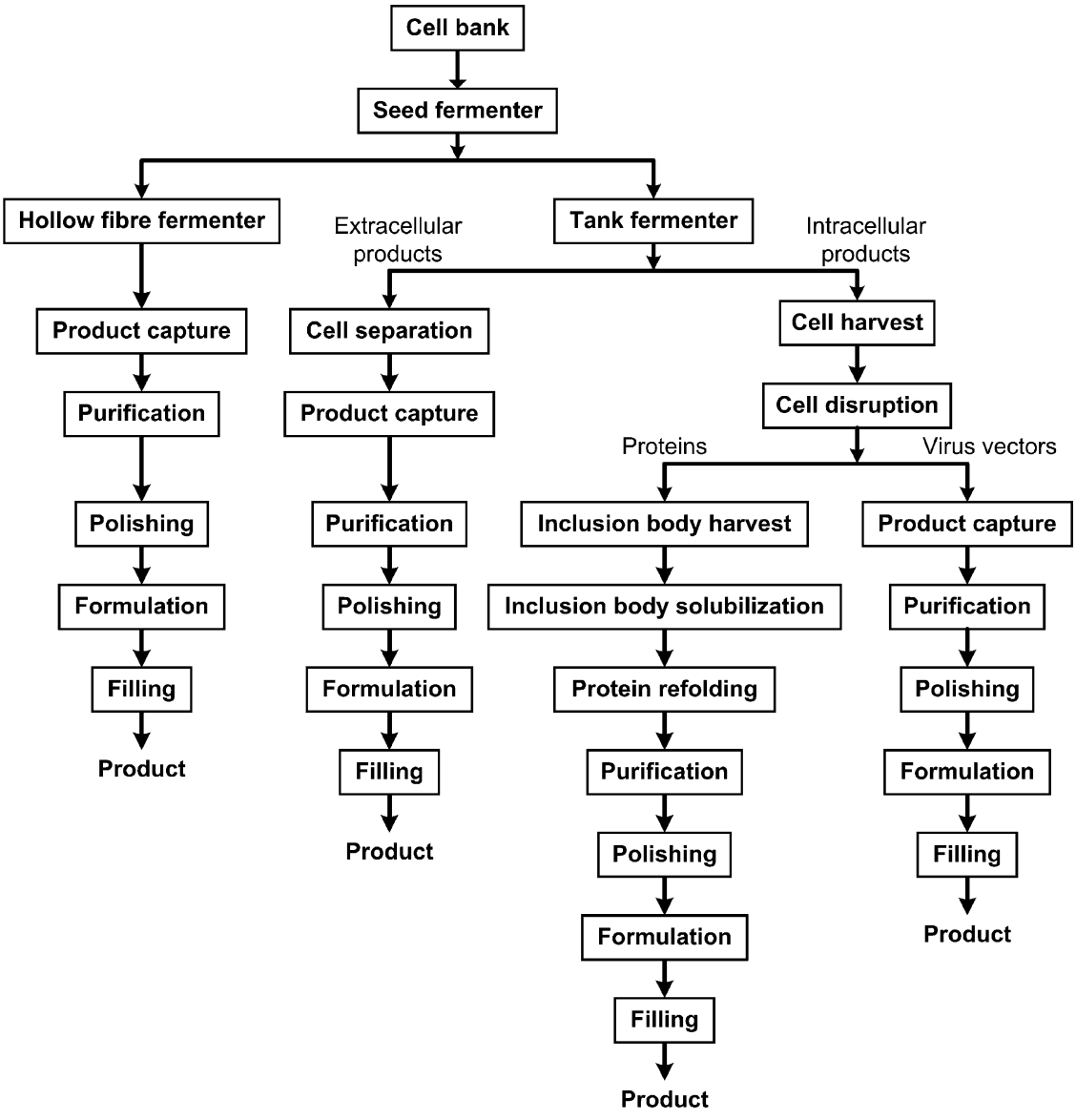

Fig. 1. Stages of biopharmaceutical manufacturing process.

mentioned as an important consideration with reference to the number of required unit operations as all media components must be completely removable from the end product. Hesse and Wagner [17] have also previously pointed out that completely defined protein free media are usually less expensive than complex media consisting of extracts. Developers should also be aware of the use of animal derived raw materials, such as serum, which is currently strictly regulated by the authorities [18].

With reference to the host cell, the developers also pointed out that the establishment of a cell bank for biopharmaceutical production is imperative. To do so, the manufacturer must present thorough documentation of the origin, i.e. the tissue, the method of isolation, culture and storage conditions, the media used for cultivation and cryopreservation [17]. Interviewees also stated, that most developers maintain a master cell bank and a working cell bank although this is not required by regulatory authorities. On the other hand, the authorities do require that the master cell bank is accurately characterized, which, according to interviewees, is expensive costing between €200,000 and 300,000.

3.2. Choosing production technologies and equipment

According to interviewees the introduction of new and improved technologies to the production of biopharmaceuticals is complex and may be expensive. Any new processing technology may face additional regulatory requirements, which may delay the production

process. Consequently, developers recommend using well-established equipment, with which authorities are familiar. The reluctance of pharmaceutical industry to change their manufacturing processes and equipment has also been recognized by FDA. Due to regulatory uncertainty caused by perceived and sometimes real regulatory hurdles pharmaceutical companies have been hesitant to introduce innovative new systems into the manufacturing sector and many manufacturing procedures are treated as being frozen. Consequently in August 2002 FDA launched a new initiative entitled 'Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach' to create a new framework for the regulatory oversight of manufacturing based on quality systems and risk management approaches that will encourage pharmaceutical manufacturers to utilize modern manufacturing tools that can be used to help ensure manufacturing quality and enable the continuous process improvement [19]. As a part of this initiative FDA has created a scientific risk-based framework entitled Process Analytical technology (PAT) to support innovation and efficiency of manufacturing process design and control and quality assurance. The goal of this framework is to ensure a predefined final product quality through enhanced understanding and control of the manufacturing process. It can be used for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials during processing. The use of PAT allows more focus to be placed on relevant multifactorial relationships among material, manufacturing process, environmental variables and their effects on quality, which provides a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk reducing strategies [20].

Host cells are usually cultivated in tank fermenters as submerged fermentations, which can be performed either in batch or fed-batch mode. The fed-batch mode, in which more nutrients can be fed during the fermentation, is capable of producing higher dell densities than batch mode. The former is thus more suitable for large-scale production as stated also by Thiry and Cingolani [21]. It was also stated that another alternative is to cultivate host cells as a supported growth in hollow fibre fermenters. However, these are not feasible for large-scale production, as their capacities are limited. Harvesting cells at the end of the fermentation requires a number of unit operations, which depend on the nature of the host cell and the desired product. Developers tend to separate host cells from the culture supernatant by centrifugation or filtration. In a hollow fibre fermenter the biomass is kept separated from the culture supernatant and cells do not need to be harvested. Extracellular products such as antibodies can be harvested directly from the culture supernatant, but intracellular products must first be released from the host cells by rupturing them. If product proteins have formed inclusion bodies, they must be dissolved and incorrectly folded proteins refolded.

As all current biopharmaceutical products are administered parenterally, sterility and non-pyrogenicity are imperative requirements for these products. Process-derived impurities including contaminants derived from the culture medium (e.g. lipids, antifoaming agents, antibiotics) and host cells (e.g. proteins and nucleic acids) and adventitious impurities including viruses, virus-like particles, bacteria, fungi, mycoplasmas, etc. are typical contaminants of biopharmaceutical processes [17]. The design of purification process is guided by regulatory authorities' requirements for product purity. The aim of purification design is to identify the main contaminants and remove them from the process stream. Conventional chromatographic purification methods such as gel filtration, ion exchange, hydrophobic interaction and affinity chromatography are widely used in the purification of biopharmaceutical products. The number of required chromatographic steps depends on the nature of the product and culture supernatant. According to interviewees, affinity chromatography is often used as the first step of purification, as it can also perform product capture. Affinity chromatography is expensive, but in the long run it is most economical, as it significantly improves the yield of the whole purification process. It was stated that this is especially important in antibody production, where the product yield in the culture supernatant is usually low. Developers added that it is also necessary to pay attention to the removal of ligand proteins, which all affinity columns tend to leak. Similarly, protein and DNA residues of the host cell must be removed. The removal of DNA is usually performed by anion exchangers, which bind DNA very strongly [22]. Hydrophobic interaction and cationic exchange chromatography can be used as additional measures. Developers often use gel filtration as the final polishing stage of purification.

3.3. Formulation poses new questions for developers and regulators

Most biopharmaceutical products on the market and development pipeline are proteins such as hormones, cytokines, vaccines and antibodies or nucleic acid-based products such as virus vectors [2,3]. As both proteins and nucleic acids are easily degraded, they have to be properly formulated to ensure the desired shelf life [23]. Consequently, the aim of formulation is to create a stabilizing environment for the product for transport and storage. Selection of excipients such as osmotic agents, buffers, antioxidants and antiadsorbents, physical state and storage conditions are critical for the success of formulation [24]. Freeze-drying was mentioned as a typical, but expensive method, commonly used for the stabilization of antibodies. However, freeze-drying can damage protein structure and thus requires the use of proper lyoprotection [24]. It was

also stated that as macromolecular biopharmaceuticals are far more complicated than conventional small molecular pharmaceuticals, their formulation often leads to case-by-case evaluation by the regulatory authorities, which may take time.

The final stage of biopharmaceutical manufacturing process is filling. As most biopharmaceutical products are currently delivered to the patient intravenously, filling has to be performed aseptically and consequently its success is critical for the success of the whole manufacturing process. However, ready to use forms such as pulmonary delivery applications, which are easier for patients to use, less invasive and do not require aseptic filling, will also be developed for specific indications.

4. Process scale-up is a challenge

Majority of interviewees regarded process scale-up as a problematic area, where it is always possible that something unexpected may happen. The success of scale-up was thought to depend on personal experience as well as on project timetables, project failures and regulatory matters. As shown in Fig. 2 the manufacturing process needs to be up-scaled at least four times during the development project: first before entering Preclinical Trials, second before entering Clinical Trials, third before entering Phase III Clinical Trials and fourth before commercial scale production. Consequently, biopharmaceuticals product developers must plan to carry out many stages simultaneously. It was also stated that the manufacturing processes can only be changed up to a certain limit. The new processes have to be similar to the original ones and their end products have to be comparable to the end products of the original processes. Thus, if the manufacturing licence has very strict process specifications it may be impossible to up scale the process at a later date.

As a part of its 'Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach'-initiative the FDA has established a mechanism for regulatory relief for changes in chemistry, manufacturing and controls (CMC) of well characterised biopharmaceuticals through the use of comparability protocols. The intensity of FDA oversight will depend on the degree of a manufacturer's product and process understanding and the robustness of the quality system controlling their process. Changes to complex

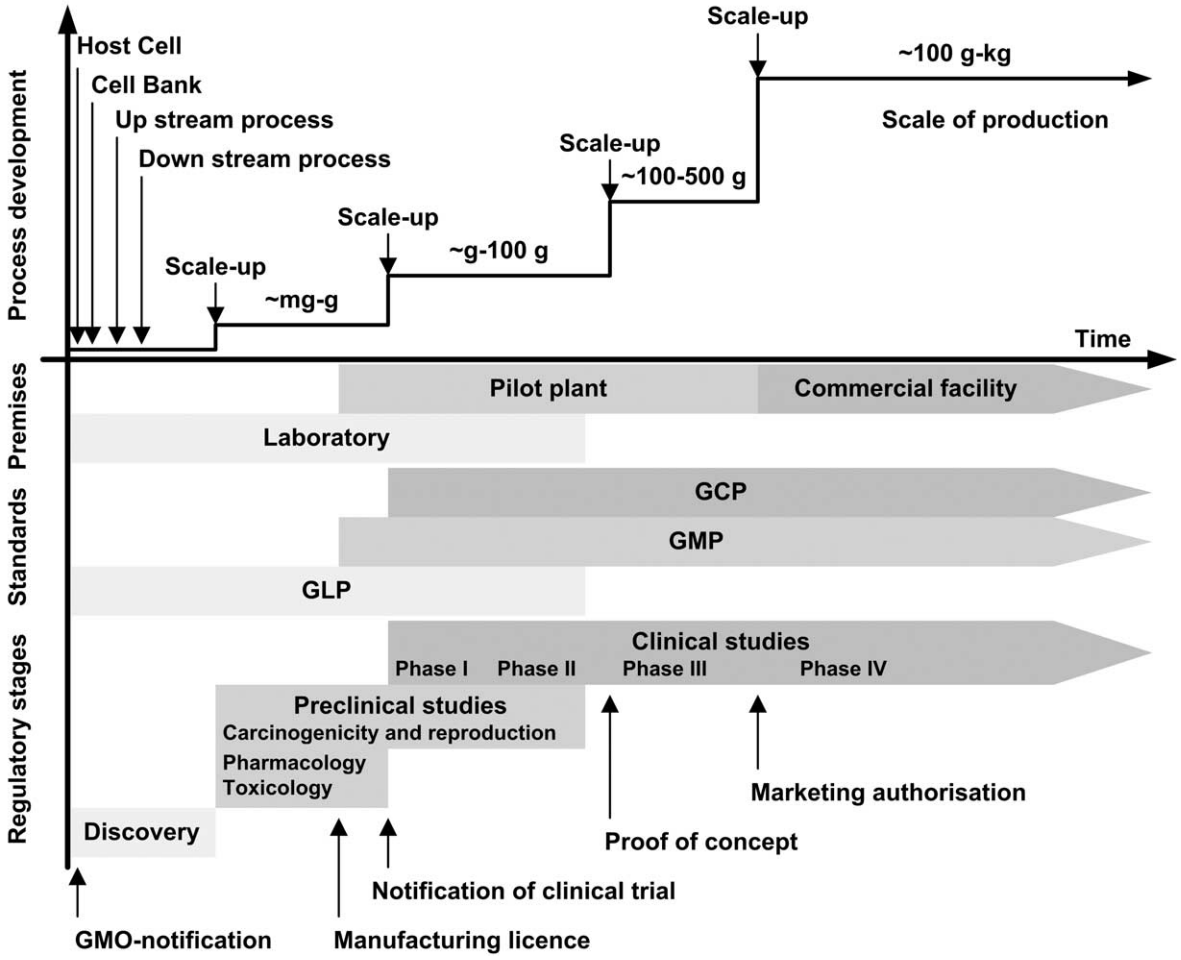

Fig. 2. A framework model for implementation of a biopharmaceutical development project.

products, products that are less well understood from a manufacturing or quality attribute perspective and complex processes will require more regulatory oversight than changes in well understood processes, which can be managed under comparability protocols. These protocols are well defined and detailed written plans for assessing the effect of specific CMC changes on the identity, strength, quality, purity and potency of a specific drug product as these factors may relate to the safety and effectiveness of the product. They describe the changes that are covered under the protocol and specify the tests and validation studies that will be performed, including the analytical procedures that will be used and acceptable limits to be achieved to demonstrate that specified CMC changes do not adversely affect the product. Comparability protocols should provide sufficient information for the authorities to determine whether the potential for an adverse effect on the product can be adequately evaluated. After reviewing the protocol the authorities determine if a specified change will fall into a less restrictive reporting category than the category for the same change implemented without an approved comparability protocol. This may facilitate the subsequent implementation and reporting of CMC changes, which could result in moving a product into distribution sooner than if a protocol were not submitted [25].

Equipment-related problems in scale-up are often due to inadequate interphase mass and heat transfer and non-uniform concentration and temperature profiles [26]. A major problem in the scale-up of submerged fermentations is the inadequate transfer of oxygen to microorganisms [27] and dissolved oxygen often becomes limiting factor in high growth rates [21]. The shape and the size of fermentor and the agitation/aeration system are critical for the success of oxygen transport [27]. Adequate mixing is especially important for ensuring that the development of disadvantageous concentration gradients can be avoided in the fermentor [28]. However, effective mixing increases also the shear forces, which may be damaging to more sensitive products. The glycosylation of glycoproteins is especially sensitive to changes in mixing and minor changes may cause variation in glycosylation pattern [24]. To be successful in scale-up, every single process change should be understood and their effect to the host cells and the product must be analysed before any further changes are introduced in to the process.

Developers tended to use tank fermenters for larger production volumes. The cultivation of cells is performed as submerged fermentations, which are up scaled by increasing the fermentation volume. If the increase in the fermentation volume is considerable, it is customary to perform the increase stepwise (20 l→80 l→400 l→2000 l→15 000 l) and analysing effects on the host cell and product after each step to avoid unexpected scale-up problems. The production capacity of hollow fibre fermenter can be up scaled by increasing the number of parallel units. However, the hollow fibre fermenter was not considered to be suitable for large-scale production, as its size is limited. Chromatographic purification processes are up scaled by increasing the cross-sectional area of the columns, which can be performed either by using columns with wider diameter or by increasing the number of parallel columns. Up to a certain scale it is also possible to increase the production capacity by increasing the rate of expression and the yield of purification.

5. Commercial scale production requires early planning

Product samples for preclinical studies can be manufactured in the laboratory by complying with Good Laboratory Practice (GLP). However, as the project proceeds to clinical studies, product samples must be manufactured in the pilot plant in compliance with Good Manufacturing Practice (GMP) (Fig. 2). According to the results of our interviews, the cost of constructing a suitable GMP facility for manufacturing purposes varies considerably. Estimates of the construction costs varied from €2000 to 4200 per m^2 and depend on the intended purpose of use of the premises. Clean areas for the manufacture of sterile medicinal products are classified as A, B, C and D, grade A having the cleanest environment [29]. It was stated that by sealing the process completely from its surroundings and using clean in place (CIP) and steam in place (SIP) systems, it is usual to carry out fermentation and down stream processing in grade D environment, which is safest for product quality as fermentation is performed in closed 'sterile' systems. A grade A zone, which is usually a laminar airflow workstation surrounded by grade B area, is required for aseptic filling of sterile intravenous products.

Manufacturing and production equipment is a considerable investment, e.g. fermenters and down-stream processing equipment and auxiliary equipment for the production of utilities such as steam, clean gases, water for injections (WFI), etc. A proper supply of WFI was considered to be a large investment, but as bioprocesses usually tend to consume large amounts of water it was emphasized that it is important to size the WFI supply large enough for increased future needs. Validation requirements increase the cost of premises and equipment. It was stated that it is possible to ease up the validation process of equipment by purchasing equipment with an installation qualification ('IQ') by the manufacturer, but this is only the smaller part of the overall validation requirement.

In 2003 there were 16 small or medium sized pharmaceutical research and development companies in Finland, of which four focused mainly on developing biopharmaceuticals (Table 2). According to published data, there were three biopharmaceuticals in the Preclinical Trials and six in the early stages of Clinical Trials, but no biopharmaceutical product had yet been taken to Phase III Clinical Trials or to production by the end of 2003. Most Finnish biopharmaceutical development companies were

Table 2
Small and medium sized Finnish pharmaceutical R&D companies, summary of main areas of interest and targets of research

Company	Main areas of interest	Main targets
ARK Therapeutics Ltd	Viral vectors, gene based medicine and diagnostic products	Malignant glioma, cachexia, blocking of veins and arteries after vascular surgery, leg ulcers and lipodystrophy syndrome
BioLigand Ltd	Bacterial vaccines, carbohydrate receptors and their ligands	Not listed
BioTie Therapies Corp.	Monoclonal antibodies, small molecule inhibitors, opioid receptor antagonists and glycobiology based products	Inflammatory diseases, impulse control disorders, infections, thrombosis, cancer and thromboembolic diseases
CTT Cancer Targeting Technologies Ltd	Anticancer drugs and drug delivery systems based on cancer specific peptides and peptide liposomes	Cancer
Finncovery Ltd	Prodrug and cyclodextrin technology, target-based drug design and synthesis	Not listed
FIT-Biotech Plc.	DNA vaccination, immuno and gene therapies, immunogens, recombinant proteins, antibodies and diagnostic products	HIV, intimal hyperplasia, thrombus formation and occlusion, restenosis, cancer, allergies, Parkinson's and dermatological diseases
Focus Inhalation Ltd	Pulmonary drug delivery: carrier based dry powder formulation technologies	Asthma, chronic obstructive pulmonary disease, cancer pain and protein delivery
Galilaeus Ltd	Polyketide drugs and fermentative production processes of active pharmaceutical ingredients	Cancer
GeneOS Ltd	Advanced drug target discovery, diagnostics development products and proprietary genomic database products	Not listed
Hormos Medical Plc.	Selective estrogen and androgen receptor modulators and hydroxysteroid dehydrogenase and aromatase inhibitors	Osteoporosis, Alzheimer's, lower urinary tract symptoms, breast and prostate cancer and cardiovascular diseases
Ipsat Therapies Ltd	Enzyme based therapies	Antibiotic-induced bacterial resistance, hospital infections, antibiotic-induced colitis and diarrhea
Juvantia Pharma Ltd	Alpha-2 antagonists, somatostatin and neuropeptide FF reseptor agonists	Parkinson's, depression, cardiovascular disorders, re-stenosis and chronic pain
Karyon Ltd	Tissue specific targeting peptides for use in diagnosis and therapy	Sarcoma, melanoma, glioma, tumour blood vessels and metastases
Lead Pharmaceuticals Ltd	Small molecule drug discovery for novel drug targets	Viral and bacterial diseases, depression, Alzheimer's and cancer
MediCel Ltd	Systems biology in drug target discovery and validation projects related to inflammatory diseases	Inflammatory and infectious diseases
Novagent Ltd	Systems for transdermal delivery of drugs	Not listed

Data obtained from public source.

self-sufficient in manufacturing capacity, although the size of their clean rooms was quite small (less than 150 m^2). In addition there were also some companies offering manufacturing services for the biopharmaceutical development industry and also some universities and polytechnics have their own clean rooms (Table 3). However, none of these companies is at this point able to manufacture products at a larger commercial scale. In fact the aim of most Finnish biopharmaceutical companies at the present is to licence out their first products.

According to interviews, the construction of a small pilot plant for biopharmaceutical production may cost at least €8 million and all required process and auxiliary equipment another €8 million. The downstream processing equipment

Table 3
Some Finnish contract manufacturers, their location and core business

Company	Location	Core business
Biovian Ltd	Turku	Contract research, development and contract manufacturing of antibodies and recombinant proteins
Medipolis GMP Ltd	Oulu	Production of clinical biomaterials
FIT Biotech Plc.	Tampere	Plasmid manufacturing services and cell bank contract manufacturing activities
Pharmatory Ltd	Oulu	Custom contract development and cGMP manufacturing of APIs and key intermediates
Pharmia Ltd	Helsinki	Contract manufacturing, packaging and other related services
Turku Polytechnic	Turku	Process development and scale up services, production of biomolecules for research, process development or diagnostic use
University of Oulu	Oulu	Facility for mass cultures of insect cells and for monoclonal antibodies producing hybridoma cells

Data obtained from public source.

alone was estimated to cost some €170,000. However, it was pointed out that by settling for lower production capacity for a start it is possible to keep the investments for process equipment between €300,000 and €500,000. On the other hand, as the construction and approval of suitable facilities and equipment for biopharmaceutical production takes time, the investment decisions for new manufacturing capacity must be made early. This presents a high risk, as investment decisions for the manufacturing capacity for Phase II Clinical Trials production have to be made before the beginning of Phase I Clinical Trials, when there is not yet necessarily any indication of the success of the product. Moreover, investments for Phase III Clinical Trials production are even larger (over €50 million) and the decision to take the project to Phase III Clinical Trials has to be made at the latest in the middle of Phase I Clinical Trials. Overall investment decisions for the commercial scale manufacturing facility should be made 4 years earlier, when the products are still in the first Phases of Clinical Trials (Fig. 2).

Some interviewees stated that although initial investments are higher, it is profitable to design certain reservations for the enlargements of premises. It is much cheaper to increase the size of the premises later if necessary. It was also suggested that a small developer company needing a clean room for small scale production could cut the investments needed for the manufacturing premises by utilizing modular clean rooms. These are commercially available and can be assembled to fit into a normal industrial production facility.

The majority of our interviewees felt that there is a need for more clean room facilities in Finland in the near future. However, evidently this will depend on the timing of projects, and if many projects enter Clinical Trials at the same time there will not be enough manufacturing capacity. On the other hand, licensing prior to Phase III Clinical Trials will reduce the need for production capacity. It was also pointed out that there will also be misinvestments, as some projects will fail. Thus there would be more free clean room capacity than needed at a reduced operating cost. Regardless of these uncertainties, the need for premises should be anticipated before the lack of premises becomes a bottleneck for product development.

5.1. Is contract manufacturing a viable alternative?

The majority of biopharmaceuticals are developed by small research oriented companies, which usually do not have the facilities for commercial manufacturing. Instead, manufacturing services from an outside contract manufacturing organization (CMO) may be utilized [7]. Interviewees did regard outsourcing as a viable alternative to companies with only one or two products in the development pipeline. For companies with multiple products in the development pipeline, outsourcing was considered as a one alternative to ease up the need for manufacturing capacity. The costs of contract manufacturing are only a fraction of the investments needed for designing, constructing, staffing, starting and validating a GMP biomanufacturing facility [30]. For most small companies, which are proceeding with clinical studies, outsourcing is often considered to be the only alternative due to financial limitations [31]. Timing was seen as one of the major problems of outsourcing, as manufacturing capacity usually has to be booked much earlier than it is needed. Another problem mentioned was that the developers' special know-how may easily flow out, as production is outsourced. Some interviewees were also concerned about the flow of information between companies. As the information tends to move faster inside the developers own company than between the developer and the CMO, thus information on production problems may become critically delayed.

However, all interviewees agreed that establishing commercial scale manufacturing, in-house or by CMO, is very risky. As the markets in Finland or even in Scandinavia are small, commercial manufacturing facilities should serve at least the European or preferably the global markets.

6. Concluding remarks

The key to success of biopharmaceuticals product development is maintaining product comparability by proactive planning and the simultaneous implementation of three main areas of the development process. First, the ability of the host cell to produce the desired product requires suitable equipment for cultivation and purification of the product. These must be carried out in a manner, which maintains the comparability of the product during subsequent scale-up processing. Second, scale-up will require the mastering of the host cells in the new environment created by scale-up equipment and technologies, where comparability must be maintained from batch-to-batch. Third, choosing to invest in production facilities or utilizing CMO services should be evaluated with reference to the own and CMO's capability and track record, the producer cell, the quality of the product aspects, the equipment necessary and the economics of scale up and commercial scale manufacturing. Finally, the product only reaches the market if regulatory demands for safety and efficacy are met, which are still the most challenging issues when the 'the product is the process'.

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