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Estonian Biotechnology Programme

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Feasibility study for an Estonian biotechnology programme

13 2010

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Feasibility study for an Estonian biotechnology programme

Final Report

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Foreword

After the revolutionary years in information and communication technologies (ICT) our conception of the world has been considerably changed. The things that we could not even dream of only a while ago have now become part of our everyday life. Nowadays satellite communications in space as well as the temperature at our homes are supervised by ICT systems.

The next breakthrough technology that could bring about an enormous turnaround is expected to be material technology (principally nanotechnology) and/or biotechnology. These technologies are believed to have the potential for significant and dominant global effects on all dimensions of life: economical, political and personal. These effects may include significant improvements in quality of human life and life span, high rates of industrial turnover, continued globalization, mixed environmental effects, etc.

Biotechnology has a deep suspected impact on other economic sectors in replacing or improving the existing products, services or technologies with new added-value of products, services and technologies.

The biotechnological applications with most potential as highlighted by recent studies and research are:

- Agriculture – plant and animal breeding technologies.
- Food industry – functional food products development, food processing technologies, food diagnostics and safety.
- Wood and paper industry – wood processing and pulping.
- Environmental protection – bioremediation.
- Healthcare industry – therapeutic products, diagnostics, drug discovery technologies.
- National defence – biodefence.

Despite ongoing optimism, a number of technical issues and hurdles have moderated confidence in the triumph of biotechnology. It has become clear that in order to achieve economic success a great number of current scientific discoveries must be upgraded by high-level scientists. It will demand a considerable amount of investments and time.

According to the Estonian research, development and innovation strategy ''Knowledge-Based Estonia 2007–2013", biotechnology is highlighted as the strategic key technology that has a potentially significant impact on Estonian economy. To contribute to the development of biotechnology in Estonia the launch of a thematic state R&D programme – Estonian Biotechnology Programme (BTP) – is provided by the aforementioned strategy.

The Ministry of Economic Affairs and Communication in cooperation with BTP programme manager commissioned a feasibility study, financed from the structural funds, to analyse the potential of biotechnology in Estonia and to give recommendations for building up BTP.

The aims of the current feasibility study were to examine the most thriving fields for Estonian biotechnology sector, the readiness level of Estonian traditional industries, the other sectors to apply biotechnological tools and methods, and Estonian biotechnological research areas from the commercialisation perspective.

The BTP is a thematic state R&D programme launched in cooperation between the Ministry of Economic Affairs and Communication, the Ministry of Education and Research, the Ministry of Agriculture, the Ministry of Environment and the Ministry of Social Affairs.

Therefore the feasibility study intended to be helpful also to audiences abroad, including policymakers in their decision making process.

The BTP as all thematic state R&D programmes is financed by the involved ministries, using structural funds according to the nature of the programme activities and needs of the programme priority development areas.

Division of Technology and Innovation
Estonian Ministry of Economic Affairs and Communication

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Abstract

The current report summarizes the results of the feasibility study for the Estonian Biotechnology Program. The Study took place from May to October 2009. The aim of the project was to find the most promising fields of interest for the Estonian biotechnology sector given the current strengths and potential both in academic and industrial sectors. During the project, extensive bibliography study and data collection were conducted including several interviews with managers of biotechnology companies, leading researchers and policymakers, a workshop with Estonian biotechnology stakeholders, a bibliometric analysis, a case-study and benchmark analysis.

The results showed that most potential biotechnology business fields in Estonia are related to food and healthcare sectors. In short- to mid-term perspective good opportunities in the field of Diagnostics, Drug discovery technologies, Food processing, Functional food as well as Food diagnostics and safety were identified. From the long-term point of view, Diagnostics and Therapeutic products were identified as promising business fields. In addition, rather feasible niche opportunities were identified in the fields of plant and animal breeding technologies as well as paper and pulping industry.

The study on Estonian R&D potential showed that the business fields closest to the market are: drug discovery, therapeutic development, environmental monitoring, diagnostics, bioprocessing and plant breeding. Research fields supporting these domains are: bioinformatics, genetics, drug discovery and environmental diagnostics.

The analysis has shown that there is a gap between fundamental research, the first identification of an innovation and its development by the industry, and therefore reinforcement of applied research and maturation phase is the main suggestion for Estonian Biotechnology Program, which includes development of patent filing & prosecution skills, business development & marketing skills, dedicated technology transfer centres in universities and institutions at international industry standards, innovation maturation support to organizations or structures, dedicated specialized seed funding to support the financing gap and focused internationally recognized centre of excellence entities aiming at entering international networks of excellence.

Executive Summary

The current report summarizes the results of the feasibility study for the Estonian Biotechnology Program. The Study took place from May to October 2009. The aim of the project was to find out the most promising fields of interest for the Estonian biotechnology sector given the current strengths and potential both in academic and industrial sectors. The analysis was to point out which biotechnology fields could promise the highest potential for future growth and where Estonian biotechnology sector could have better advantages to gain from the growth, also to discover unused potential of biotechnology in order to enhance the efficiency of Estonian private and public sectors, where efforts could have the strongest impact on the competitiveness of the state, the effectiveness of economy and the welfare of society.

During the project, 7 sectors and 14 business fields relevant to the Estonian context were analyzed, in addition the business potential and maturity level of Estonian research areas were analyzed. As a result of the analysis, policy recommendations for the Estonian Biotechnology Program were made for fostering the most promising fields and technologies for Estonia.

Hereby the most important conclusions of the Study are highlighted:

Most Promising Business Fields

The business field analysis was conducted using data from extensive bibliography study and data collection which included

- several previous Estonian and international studies and analyses;
- 22 interviews with managers of biotechnology companies, leading researchers and policymakers;
- a workshop with Estonian biotechnology stakeholders;
- a bibliometric and patent analysis;
- a case study and benchmark analysis.

The following figure gives a global overview of the business field positioning and their potential for Estonia. On the horizontal axis, the value and market potential of the field for Estonia is evaluated and on the vertical axis, Estonia's performance is mapped. Under the Estonian performance evaluation, the existence of a critical mass of scientists and industry, as well as the research and development maturity, were analyzed. Under the value and market potential evaluation for Estonia, international and regional market size as well as international competition and barriers for entering the market were considered. The positioning on the matrix was developed by comparing different business fields to each other, meaning that business fields were positioned according to qualitative evaluations. The conclusions of the analysis of business fields, presented after the matrix figure, summarize the rationale of the positioning of each business field, the analysis of the business fields being described in more detail in the first chapter of the report.

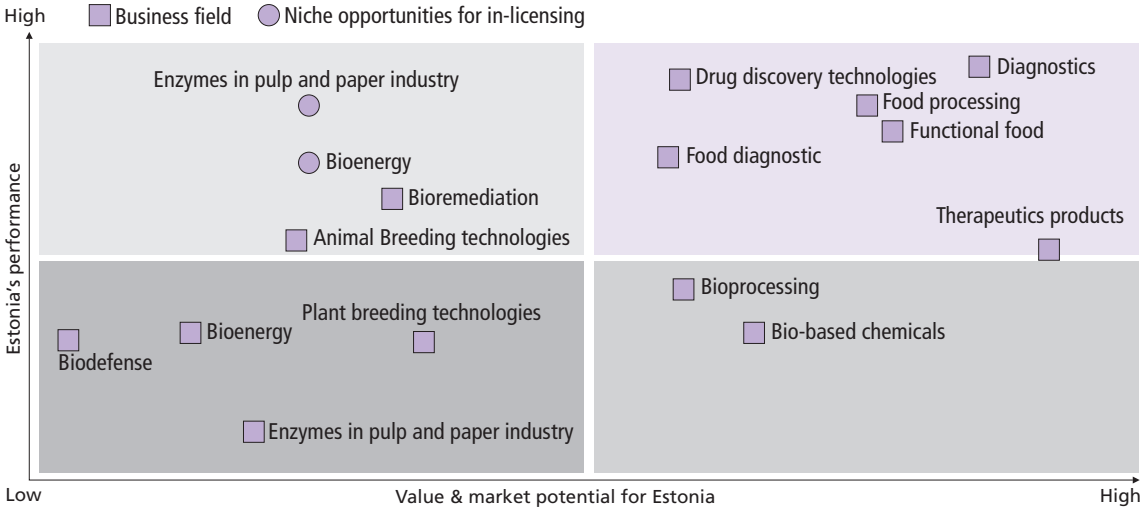

Figure 1: Estonian potential in different business fields

The results showed that the most potential business fields in Estonian biotechnology are related to food and healthcare sectors. In short- to mid-term perspective good opportunities in the field of Diagnostics, Drug discovery technologies, Food processing, Functional food as well as Food diagnostics and safety were identified. From a long-term point of view, Diagnostics and Therapeutic products were identified as promising business fields. Additionally, rather feasible niche opportunities were identified in the fields of plant and animal breeding technologies as well as paper and pulping industry. The following section elaborates on each business field in more detail.

Priority Targets

Functional Food (FF) Business Field:

The functional food business field, and more generally, the food industry represent a real opportunity for growth in Estonia. The country can rely on a critical mass of functional food industry companies having already partially turned into a knowledge-based economy system. This field is supported by a strong and applied research community, including two competence centres, with a primary experience of deal making with the industry. The market size for functional ingredients and functional food is remarkably high and quickly growing. Although the market is dominated by big players, the current need of these big players for novel innovative ingredients is obvious and results in the increasing number of alliances and license agreements between big players and small companies, or even applied academic research, leading to major opportunities for Estonia. The remaining challenges regarding this business field will be to further develop the practice of patent filing of inventions, with more numerous patent skills at both academic and industry level, as well as to establish the right proof of concept corresponding to the acceptable industrial in-licensing standards and to license out the innovation through solid and experience business development skills.

Food Processing (FP) Business Field:

The food processing industry is clearly a more mature business field in Estonia, with critical mass at both industry and academic levels, which need to be supported to further turn into a sustainable business field using biotechnologies on a regular basis. Companies and institutions have started to integrate the central role of patent filing and prosecution as a key success factor and this has to be further supported. Both processed and packaged food markets as well as the industrial food enzyme market are considered as huge markets with significant constant growths. These markets lead to a significant amount of short-term in-licensing opportunities for Estonia with food enzymes or food processing technologies to boost traditional industry towards new innovative products on the one hand, and mid-term innovative processed product development opportunities for further commercialization at both national and international levels on the other hand.

Food Diagnostics and Safety (FD) Business Field:

The food diagnostics business field is in between the food industry business and the diagnostics tools and technologies business, both of them being genuine strengths in Estonia. On the one hand, diagnostics tools and technologies bring technological support to accelerate the applicability of such technologies to food industry and to help overcome bottlenecks such as integration of data (bioinformatics), standardization and development of portable systems (biosensors, lab-on-chip). On the other hand, the food diagnostics field benefits from the growing safety concerns of the population and regulatory authorities about the quality and healthy nature of current processed food as well as from the growing consumption of fresh fruits and vegetables. This convergence represents a good opportunity to build upon existing strengths to develop and build a new emerging and promising business field on a solid basis.

Therapeutic Products Business Field:

This field can be considered as a high added value, long-term opportunity for Estonia as long as this field is only built upon cutting edge, new classes of products (there is very limited interest in terms of differentiation for "me better" or "me too" therapeutic products taking into consideration the massive and highly active competition from large international companies and start ups). Indeed, a critical mass in this field does exist at both industry and academic level with the emerging awareness of the importance of industrial property, the support from internationally recognized opinion leaders and the important number of projects being submitted or ongoing. However, the long-term characteristics of this field reinforce the crucial need to secure early-stage therapeutic projects through industrial property, licensing and technology transfer and early development best practices (aligned with industrial standards) through a long-term and strong support for cutting edge solutions.

Diagnostics Business Field:

The diagnostics field is certainly a very potent short- to mid-term opportunity for Estonia with long-term perspectives as well. The strong critical mass at industry and academic levels, supported by internationally recognized key opinion leaders and an important number of projects, is reinforced by the international context of deep shift in the healthcare management from pure curative solutions to prevention through early diagnosis

and therapeutic monitoring in all major and minor therapeutic areas (central nervous system, oncology, cardiovascular, infertility, autoimmune diseases, etc). This field even benefits from the strengths of Estonia in bioinformatics and genetics to overcome bottlenecks such as integration, treatment and interpretation of the generated data and standardization.

Drug Discovery Technologies Business Field:
Even though this field is not the largest in value and volume, although high and growing, this field is probably one of the shortest terms, strongest and most adapted biotech business fields in Estonia due to its positioning at the early stage level of innovation development, as well as its compatibility with mixed services and product development business models. This field is strongly supported by an applied research workforce in bioinformatics, genetics and physics, as well as a critical mass in fundamental research. This field is relatively well established (in terms of industrial property, licensing or commercialization) to allow the sustainability of the system.

Niche opportunities / Quick Wins (short-term)
Bioremediation Business Field:
The bioremediation business field is essentially represented at the academic level as no company has been identified as especially involved in bioremediation. However, this field may well benefit from other complementary competences that significantly exist in Estonia such as microbiology, metagenomics, bioinformatics, environment monitoring and management. In addition, this field is strongly supported by the government as well as the EU and at the same time, even emerging countries are feeling more and more concerned with sustainable development. At the international level, bioremediation is an existing but still largely innovative rapidly developing industry. Despite obvious technological challenges such as the scale up of a particular technology (e.g. metagenomic approach in environmental monitoring) to field operations, this field could be a short- to mid-term opportunity for Estonia as there are already ongoing applied research projects on microbial strains for waste management and environmental monitoring, which could drive this sector at national level targeting both national and international markets.

Animal Breeding Technologies (ABT) Business Field:
The ABT sector is characterized by an existing, relatively important and structured animal breeding system with existing research activities on biotechnological animal breeding (including transgenic animal creation, although not applied to agriculture). The existence of an Estonian diagnostics, genetics and bioinformatics workforce is synergistic with the potential to develop molecular marker assisted selection tools and services for animal breeding. This is even reinforced by the willingness of the European population for healthier food and agriculture environmental protection addressable through animal breeding. However, the complexity of the regulatory environment, the early stage of technological development of molecular marker assisted selection tools for animal breeding, as well as the difficulty to create a market positioning as a new entrant, lead to envisage the ABT business field as a niche opportunity. Development should be considered with the objective of marketing molecular marker assisted selection tools and high-tech services in animal breeding for international markets, rather than creating transgenic animals for agriculture (transgenic animal creation for therapeutic molecule manufacturing purposes has been considered in the bioprocessing business field).

Niche Opportunity in the Paper and Pulp Industry
This field has to be considered rather as a good niche opportunity for the Estonian forestry sector as neither academic or private research in this field nor existing or emerging biotechnology industry have been identified. Indeed, Estonia owns important forest resources and has currently a mature forestry industry which could greatly benefit from the acquisition of pulp and paper enzymes from international industries for the improvement of product quality and productivity of this industry in the short term as well as modernization and more knowledgeable industry with higher added value in the longer term.

Niche Opportunity in Bioenergy
Estonia may consider the bioenergy field as an opportunity for in-licensing existing patented technologies from other countries (USA or Western Europe for instance) for national or regional (e.g. Baltic countries) markets and energetic independency purposes only, the competition being too high in this field. Indeed, even existing Western European companies have difficulties in resisting the competition of US-based companies.

Mid- to Long-term Initiatives (Need to identify competitive advantages)
Bio-based Chemicals (BBC) Business Field:
This field can be set up on the basis of strong microbiology and genetics competences and large existing national cellulosic resources. The supporting technologies, enzymatic degradations of cellulosic feedstock, are common to this field and the bioenergy business field allowing focused and synergistic efforts while leading

to very large and fast-growing markets. This field even benefits from the sustainable development trend for more environmentally friendly and efficient processes in multiple industrial applications. However, this field being still at a very early stage of maturation and the international competition being rather high, it can only be considered as a long-term opportunity requiring further technological development to achieve cost efficient cellulosic feedstock transformation.

Bioprocessing Business Field:
This field is driven in Estonia by existing research activities both at industry and academic research levels leading to a promising potential of the area only if the efforts are exclusively focused on certain complex and highly innovative bioprocessing technologies such as stem cell production or cutting edge new bioprocessing solutions. Classical bioprocessing solutions for manufacturing services of antibodies or proteins should be left to emerging low labour cost countries such as China and India.

Secondary interest fields
Plant Breeding Technologies (PBT) Business Field:
The PBT business field in Estonia is mainly centred on competences in traditional breeding, plant molecular physiology, as well as genetics and virology. However, a scientific expertise is currently emerging in advanced breeding techniques and more particularly in molecular marker assisted selection. The global international environment of plant breeding is clearly dominated and driven by genetically modified organisms (GMOs), large companies and large countries being deeply involved. However, Europe is highly uncertain in terms of regulatory context for GMOs and the public is generally not supportive of such types of products, leading to a rather limited potential of GMO development and commercialization in Europe. Taking into account the specific development conditions needed in GMOs breeding (e.g. outdoors breeding), the concept of keeping the research in Estonia to commercialize outside of Europe has very limited possibilities of success. Therefore, this non-traditional PBT business field does not represent a priority for Estonia except the niche opportunity of molecular marker assisted selection that could be improved up to an excellence level able to be further commercialized at both national and international levels as high-tech services.

Enzymes in Pulp and Paper (EPP) business field:
Due to the lack of identified academic or private research in this field as well as no existing or emerging biotechnology related industry, this field has to be considered rather as a niche opportunity for Estonia in specific in-licensing cases.

Bioenergy Business Field:
This field is correlated with the massive and growing demand for renewable energy at international level. In Estonia, despite a critical mass of traditional biofuel energy industry (combustion system), a rather small workforce at both academic and industry level is concerned by biotechnology related biofuel. In addition, the incredibly high pressure from the US competition on this topic has resulted in a huge threat for well-established European companies and is therefore ever more threatening for the new entrant that Estonia might be. As a consequence, Estonia may consider this field as an opportunity for in-licensing existing technologies from other countries/companies (USA or Western Europe for instance) for national or regional (e.g. Baltic countries) markets and energetic independence purposes only.

Biodefense Business Field:
Biodefense is a field where no activity has been identified in Estonia. However, certain competences such as bioinformatics, biosensors, genetics and diagnostics, which are very strong locally, could easily be adapted to such topics. The strong international competition as well as the governmentally driven nature of this field leads to suggest that it is not a primary opportunity for Estonia, although it might be considered as an opportunity for political reasons.

The Evaluation of the Estonian Biotechnological Research Areas

The evaluation of the Estonian biotechnological research areas has been based on the ETIS database, which includes over 4,000 publications corresponding to over 500 researchers in the field of biotechnology. Publications were ranked according to the impact factors of the journals they were published in. Analysis was then carried out with the researchers who had published in top journals as first or last author. Analysis demonstrated the following points:

The presence of high-quality internationally recognized Estonian research in the biotechnology field indicates a potential for generation of added-value results transferable to the market (given that the required technology maturation tools are existent and efficient). Furthermore, existence of internationally recognized scientists

contributes to bringing to the related business fields the international scientific credibility necessary for a competitive position in the global market.

According to the analysis, the business fields closest to the market are, in decreasing order: drug discovery, therapeutic development, environmental monitoring, diagnostics, bioprocessing and plant breeding. Research fields supporting these domains are: bioinformatics, genetics, drug discovery, diagnostics and environmental diagnostics.

Estonia can mostly rely on recognized research in the areas of neurosciences, environment, oncology, autoimmune & inflammation disorders and, to a more limited extent, infectious disease, cardiovascular, reproductive medicine and phytobiology; with applications in the therapeutic development and diagnostics business fields and, in a more limited manner, environmental monitoring and bioremediation, plant breeding and drug delivery.

Policy Recommendations for the Estonian Biotechnology Program

Main shortages in Estonian biotechnology sector were identified and policy recommendations were drawn based on interviews, a workshop, several case studies and internal knowledge of evaluation experts.

The analysis showed that there exists a certain level of awareness of the current challenges related to biotechnology at both industry and academic levels (depending on the fields). The observed willingness to overcome these barriers is an important driver for the Estonian biotech ecosystem. However, the whole Estonian biotechnology ecosystem is suffering from gaps preventing it from moving towards a sustainable and economically viable system.

There is a lack of companies with strong industrial property protection able to compete with the position of the companies from Western Europe, North America and emerging countries leading to a very limited potential for export commercialization as well as restricted existence of companies with non-service-based business models.

In addition, a lack of financial investment able to support product development pushes Estonian Biotech companies towards the development of revenue-based business models such as service-based business models, thus limiting considerably the potential of development of a high added-value biotech industry.

At the institutional level, a lack of methodology in supporting the biotechnology industry sector (e.g. absence of a specialized national authority for priority field selection and associated support) allows only limited coordination of general efforts.
A limited workforce in every biotech sub-field is observed leading to the need for more specific trainings, additional graduate people including Ph.D. to support any growth of this field.

The lack of biotech-specific marketing, business development and licensing profiles with good understanding of industrial property issues, processes and regulatory situation has also been identified requiring specific training or international joint MBAs.

Therefore key success factors for the Estonian Biotechnology Program for overcoming these shortcomings are:

- Ability to take the decision to focus on certain business fields in terms of national support
- Availability of patent filing & prosecution skills (patent filing, prosecution, litigation) dedicated to biotechnology subjects at both academic and industry level with international experience
- Availability of business development & marketing skills dedicated to industry business fields (food, energy, environment, health) in both companies and technology transfer offices from universities and institutions
- Dedicated technology transfer offices in universities and institutions working under international standards (see VIB case study)
- Innovation maturation support organization or structure to fill the gap between research innovation and applied development through project selection, maturation and development according to industry standards. The objective is to obtain the proof of concept awaited by the industry for out-licensing by the industry or investment by financial institutions.
- Awareness of the strategic positioning and importance of industrial/intellectual property
- International research workforce or workforce recognized and integrated in international networks

- Ability to publish in journals with high impact factors including in clinical research subjects
- Dedicated specialized seed funding (with good understanding of the correlated timelines and ROI) to support the innovation financing gap
- Evolution from pure service-based business models to mixed services and product development oriented business models with major efforts put on product or high-tech innovative services with high added value.
- Building internationally recognized focused center of excellence entities aiming at entering international networks of excellence

Introduction

Overview of the Project

Current feasibility study is carried out in order to give input to Estonian Biotechnology Program. The goal of the project was to find out the most promising focuses for Estonian biotechnology sector given the current strengths and potential both in academic and industrial sectors. In the current report the given aspects have been analyzed more deeply in order to propose most relevant focuses and necessary political measures for the Estonian Biotechnology Program.

During the project, 7 sectors and 14 business fields relevant to Estonian context were analyzed in detail, and in addition, the business potential and maturity level of Estonian research areas were analyzed. As a result of the analysis, policy recommendations for the Estonian Biotechnology Program were made for fostering the most promising fields and technologies for Estonia.

Applied Methodology

Feasibility Study for the Estonian Biotechnology Program took place from May to October 2009. Work regarding the project was divided into three stages:

- Project planning
- Information gathering and analysis
- Synthesis and presentation of the results.

Project Planning
In the project-planning phase, a Kick-Off meeting was held in which expectations of stakeholders of the Biotech Program were specified. The Kick-Off meeting took place on 11th May 2009. As a result of the meeting a kick-off report was delivered to the client specifying Ernst & Young's approach.

Information Gathering and Analysis
The information-gathering phase covered secondary data collection, the program of interviews and a workshop held with Estonian Biotech stakeholders, and the analysis of Estonian R&D and other databases.

Secondary Data Analysis
Earlier Estonian and international sources were analyzed for putting together the present study. E&Y internal sources and available studies dealing with life sciences from the Ernst & Young's Center for Business Knowledge, bibliography provided by the client (e.g. previous studies related to Estonia) and other external sources (Datamonitor, Frost & Sullivan, Business Insights, …) were used.

Interviews
22 interviews were conducted with Estonian biotechnology industrial and academic stakeholders (from fields such as agriculture, food processing, wood processing and pulping, chemical industry, environmental technologies, energy supply, healthcare services, national security etc). Interviews were conducted in a semi-structured way with the managers of biotechnology companies and leading researchers to identify the challenges and potential of the sector and to formulate recommendations for both the public and private sectors:

Table 1: List of interviewed people

	Name	*Structure*	*Function*	*Date*
1	Marti Riistop	Estonian Forest Industries Association	Deputy managing	29-May
2	Dr. Liina Eek Dr. Jüri Truusa	Ministry of Environment	Department of Environmental management and technology	29-May
3	Erki Mölder	Quattromed	CEO	29-May
4	Lauri Raid	Estonian Cell	Main manager	9-Jun
5	Pr. Paavo Kaimre Kalev Jõgiste	Estonian University of Life Sciences – Institute of Forestry and Rural Engineering	Director; Institute of Forestry and Rural Engineering	10-Jun
6	Dr. Katrin Kaarna	Quintiles	Director, Clinical Operations	10-Jun

	Name	Structure	Function	Date
7	Pr. Ain Heinaru	University of Tartu Institute of molecular and cell biology	Dean, Faculty of Biology and Geography	10-Jun
8	Dr. Andrus Tasa	Tartu Biotechnology Park & TBD Biodiscovery	CEO	10-Jun
9	Dr. Toomas Neuman	TTU & Protobios & FibroTX (& Cemines (US)) & CCCR (Head of diagnostics research)	CEO	11-Jun
10	Pr. Madis Metsis	TTU & Biotap Ou & Toolbox Ou & CC reproductive medicine partner	CEO	11-Jun
11	Kristi Pärn	Tere Ltd	Product development manager	11-Jun
12	Urmas Sannik	CC of food and fermentation technologies	Director	11-Jun
13	Jaano Haidla	Graanul Invest	Production and raw materials manager	11-Jun
14	Ilmar Pralla	EAS	Director of the Innovation division	12-Jun
15	Aavo Isak	Pelltech	Member of board	12-Jun
16	Indrek Kask	Asper Biotech	Head of business development	12-Jun
17	Aret Vooremaë	Ministry of Agriculture	Head of R&D department	18-Jun
18	Tarmo Kivi	Celecure	CEO	19-Jun
19	Riin Ehin	Cancer Competence Center	Manager	19-Jun
20	Mart Saarma	University of Helsinki	Director of the Institute of biotechnology	25-Jun
21	Andres Salumets	University of Tartu/ Fertilitas/	Senior Scientist of Institute of Molecular and Cell Biology/	17-Sep
22	Sulev Kõks	University of Tartu Hospital/ University of Tartu	Vice-dean of medical faculty	30-Sep

Workshop with Estonian Biotech Stakeholders

A half-a-day workshop with major biotechnology stakeholders took place on 6th July 2009. The aim of the workshop was to identify short, mid- and long-term innovative biotech initiatives within different industries and to validate & prioritize these initiatives.

Table 2: List of workshop participants

	Name	Organization
1	Erki Mölder	Estonian Biotechnology Association
2	Madis Metsis	OÜ BiotaP, TTU
3	Kalev Jõgiste	Estonian University of Life Sciences (Tartu)
4	Märt Riistop	Estonian Forest Industries Association
5	Raivo Vilu	Tallinn University of Technology
6	Erkki Truve	Composer of Estonian Biotech Strategy
7	Meelis Tambla	OÜ NordBioChem
8	Mare Reiman	Tere
9	Toomas Paalme	TTU
10	Ülle Jaakma	Estonian University of Life Sciences
11	Toomas Veidebaum	NATIONAL Institute for Health Development
12	Maarika Merirand	Competence Centre for Cancer Research
13	Jaanus Pikani	Tartu Biotechnology Park AS
14	Elli Pärna	Estonian University of Life Sciences – Department of animal genetics and breeding
15	Jaak Vilo	Quretec
16	Malle Mandre	Estonian University of Life Sciences

Review of Publications of the Major High Potential Research Groups

An extensive bibliometric analysis based on the ETIS database was undergone to map the potential of Estonian research topics. More than 4,000 biotech-related publications with more than 500 scientists were taken as a starting point of this analysis. The methodology is described in more detail in section 3 of the report.

Case Studies and Benchmarks
Different case studies were presented during the project: five in the field of structuring equipments /investments; two case studies around R&D maturation and economic valuation of projects. There was also benchmarking with different international clusters with similarities to Estonia performed with lessons learned and objectives for Estonia. Some of the case studies have been integrated in the report; others have been delivered to the Client in the interim report.

Synthesis and presentation of the results
A global synthesis of the whole analysis was performed. The results of this analysis are presented in the current report. A presentation was also held to the biotech stakeholders to conclude the results of the project.

1 Technology Transfer of Modern Biotechnology

1.1 Industry 1: Agriculture and Food Processing

1.1.1 Plant Breeding Technologies

Introduction[1]

Definition of the Field
Plant breeding aims at improving traits of the plant for agricultural use (productivity, disease resistance, adaptation to environmental conditions and/or quality). The process is based on selecting the plants holding the desired traits, thus implying changes of genetics of the plants to better meet human needs. Plant breeding has been developed for thousands of years and is still perceived today as an essential method by number of international development agencies, especially concerning the security of foods. Examples of the benefits the plant breeding can bring to different actors:

- For farmers: improved crop performance (higher yield, pest and disease resistance, drought resistance, etc), extended growing season, possibility of novel crop production, higher energy content forage
- For the environment: reduced agrochemical use, renewable and cleaner feedstock for industry and energy;
- For the food industry: improved processing quality, improved storage characteristics, extended supply season through the extended growing seasons, reduced need for chemical inputs;
- For consumers: natural toxins-free plants, reduced allergenicity, improved taste and preservation qualities, improved nutritional contents.

Plant breeding may also be applied to forest and flower species, to obtain the same desired traits: productivity, disease resistance, and adaptation to environmental conditions and/or quality. Furthermore, the most advanced genetic techniques are enabling the development of plants for novel uses e.g. plants for energy or chemical production, or plants to produce pharmaceuticals. Research on the subject is ongoing, both in public and private structures but to the exception of crops for biofuels, very few of these new solutions have reached the market.

Different techniques have been developed for plant breeding:
Plant breeding was created with farming, when farmers selected the seeds from the best plants for the next generation. Over the centuries, this selection process has become more scientifically based, mainly because of the growing understanding of genetics and hereditary transmission of traits and the development of new technologies. Different techniques have been developed to enhance the speed, accuracy and scope of the breeding process.

1. Traditional breeding
Traditional breeding selects new varieties based on parent pedigree and phenotypes. In conventional breeding, selected parent plants from different varieties of the same species, or from different species, are cross-pollinated to combine desired traits in the next generation. This technique is lengthy and necessitates the production of hundreds of thousands of plants in successive generations. Furthermore, gene pyramiding is relatively uncontrolled.

- Novel ways have been found to improve the process, including:
- Parallel selection programs in the Northern and Southern Hemispheres
- Single seed descent
- Tissue culture
- Protoplast fusion
- Embryo rescue and assisted pollination
- Double haploid breeding

2. Breeding based on latest developments in genetic science
Breeding programs are beneficiating from the latest developments in genetic science to enlarge their scope, to improve their precision and to speed up the process. Although the parent pedigree and phenotypes are still used to create new varieties, the genotypes and molecular markers are additionally used for the selection criteria.

1 *Plant breeding, the business and science of crop improvement,* British Society of Plant Breeders

- Genome mapping of the crop species helps to broaden the scope and precision of the current breeding programs. Indeed, the mapping has enabled scientists to identify the exact position and function of the individual genes of the plant.
- Marker assisted breeding uses molecular/gene markers to follow the transmission of the desired trait through generations, and hence, to win time through the early detection and to increase productivity of selection through the improved precision.
- GMO technique is a modification of the genome of the plant through genetic manipulations, i.e. the integration of a foreign gene conferring a special trait, or the deletion of an existing trait. This allows a specific gene to be expressed without the introduction of unwanted characteristics. It also extends the range of the possible characters to be introduced in a variety.

Examples of Products and Services

- The main products currently on the market include seeds, young plants, shrubs and other planting material.
- These examples include: potatoes resistant to blight; cereals resistant to yellow mosaic; cauliflower that ripens more uniformly, enabling mechanized harvesting operations; cereals with shorter straws and semi-leafless peas for higher yields and improved standing power; field vegetables resistant to frost; improved oilseed rape for high protein meal for animal feed; compact, hard-wearing grass, quick to regenerate after wear and tear for soccer fields.
- Services are also provided for all the steps of the creation for a new variety: seed production (including off-season nurseries), crossing nurseries, maturity separations, yield tests, double-haploid production, phenotyping, genotyping, DNA extraction, transgenic testing, MAS, etc.

International Business Potential[2]

International Market Size and Growth

The plant breeding sector is extremely dispersed, varying form large agro groups and cooperatives to small producers. Few are active on the global plant breeding market. As an indication, 60 plant breeding companies are active in UK and the plant breeding sector employs 5,000 people with an additional 5,000 jobs in seed production and distribution.

Numbers are much clearer concerning the main biotech market in plant breeding: GMOs. Global sales of the transgenic seeds were projected to reach US$8 billion by 2009. Plantings of the genetic crops increase at a rate of 10 to 20% a year.

Currently, only four species are significantly grown as GMOs for herbicide and insect resistance traits:

- soybean (64% of grown ha are biotech)
- maize (24% of grown ha are biotech)
- cotton (43% of grown ha are biotech)
- canola (20% of grown ha are biotech).

However, extensions to rice and wheat are expected presently. The largest producers of these species (producing more than 10 million ha each) are the United States of America (57.7 million ha), Argentina (19.1 million ha) and Brazil (15 million ha). Other important producers include Canada, India, China, Paraguay and South Africa.

Trends and Developments

- GMOs have the advantage to give more productivity, as there is a reduced amount of loss in agricultural production. They also have a better environmental impact because they decrease the need to fertilize, which is one of the main causes of greenhouse rejection in agriculture (agriculture contributes about 14% of total greenhouse gas emissions). This diminution of the gases gives a financial advantage to companies, due to benefits from Carbone credit sales market which is growing and currently evaluated to be worth approximately US$30 billion.
- In the upcoming years, the market of the genetically modified plants (GMO plants) will broaden; by enlarging it improves the agronomic behaviour of plants (input traits) or improves the yield in terms of quantity, quality, and product specification.

2 *Biotech 2009 – Life Sciences: navigating the sea change*, Burrill & Company, 2009
Clive James 2008, in *Biotech 2009 – Life Sciences: navigating the sea change*, Burrill & Company, 2009
Plant Breeding in the US private sector, Fred Bliss, 2006, HortScience Vol. 41(1)
Plant breeding, the business and science of crop improvement, British Society of Plant Breeders

- As indicated above, the cultivation of the transgenic crops is currently limited to maize, soybean, cotton and canola, but soon it will certainly be extended to rice and wheat. To date, the most commercial transgenic crops are "triple stacks", which means three modifications of the genes, but engineering an eight stack plants is intended by the end of the decade. In addition to transgenic crops, growing interest can be noted for GMO plants with the industrial value, e.g. renewable feedstock for the production of the engineered products, such as the modified starches.
- Nowadays, biotech companies seem to move from the first-generation traits (insect resistance and herbicide tolerance) to the second-generation traits, hence the benefits, not just to the farmers but also to the larger public are expected to increase exponentially.

Important International Market Participants[3]

- Today, six major corporations hold approximately 70% of the industrial property (IP) rights in the United States and Europe with regard to the genome identification and the gene expression in plants, some of which include basic tools.
- These six major corporations are Monsanto, Syngenta, Dow Agrosciences and DuPont from the United States; and Bayer CropScience and BASF Plant Science from Europe. To date, research in corporations and research institutions in the United States and Europe are focusing on certain crops, such as corn, cotton, soybean, and rapeseed (for canola oil).
- The United States is the leader in transgenic crop growing methodology. Among others, Monsanto, a US-based multinational company, is the world's leading producer of genetically engineered seed and also the leading producer of herbicide glyphosate marketed as "Roundup". Monsanto revenues reached US$11,365 billion in 2008.

Time to Market[4]

- It is estimated that it takes an average of 10 years and about US$100 million to bring a new biotech product to the market.

Identified Bottlenecks[5]

- GMO suffers from an extensive cost of research. There is also a lack of clarity in the positions taken by the authorities, especially in Europe, where the EU grants only few approvals.
- GMO has an important image problem. In particular, a significant part of the public opinion has concerns about the consequences of GMO on health, and the danger of involuntary dissemination of genes. GMO can also be opposed by some religious convictions. Furthermore, there is a fear of unfair economic models, especially linked to industrial property rights (IPR) that could affect the market place, especially in the developing countries and small structures.
- Very few plant genomes are sequenced, leading to the lack of genetic knowledge (however, this is changing and numerous plants are in the sequencing pipeline: potato, soybean, tomato, cotton etc.).

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation[6]

Plant breeding in Estonia is performed by public institutions:

- The Jõgeva Plant Breeding Institute is responsible for crop breeding of the main crops grown in Estonia (cereals and legumes, hay plants, potatoes, vegetables), maintenance breeding of registered varieties, the production of breeders' seed, and the preservation of the genetic resources.
- The Estonian Research Institute of Agriculture is focused on research and development, including the plant breeding, but has also disseminated some of its developed products (disease eradicated potato seeds & plants).
- The Centre of Forest Protection and Silviculture is responsible for the forest seed management and forest tree breeding.
- The Department of gene technology group at TTU is providing molecular marker assisted selection (MAS) services.

No private company doing any active plant breeding (traditional or non-traditional) or any research and development in that domain has been identified. Agro companies in Estonia are mainly selling/distributing products. Regarding research and development, they carry out solely field tests to make sure the varieties developed abroad are suitable for the conditions of Estonian (short growing season, rainy climate).

3 *Biotech 2009 – Life Sciences: Navigating the Sea Change*, Burrill & Company, 2009
4 Ernst & Young internal experts
5 *Biotech 2009 – Life Sciences: Navigating the Sea Change*, Burrill & Company, 2009
6 Interviews, Institution and company websites, European & US patent agency, http://www.biotech.ee, http://www.estonianbiotech.com, ETIS database, http://www.biotechgate.com

Examples of the companies with the potential to be active in this industry
Existing companies with the potential to become active are mainly the existing agro-companies that would have the potential to conduct research in plant breeding. Some examples include:

- Baltic Agro AS (previous name Kemira GrowHow AS) 90% belongs to the Danish agricultural association DLA. Revenue reached the level of US$132 million. Baltic Agro is an important company in plant fertilizers, seeds and corn market in Estonia and Baltic countries.

Supporting Research and Development for the field[7]
A number of research activities have been conducted in plant breeding (including the usage of biotechnologies, such as MAS). As an illustration, the ETIS database notes more than 50 publications for the search word «plant breeding».

Furthermore, the presented research performed in plant biology (molecular phytobiology, plant virology) is a necessary requisite and supports plant breeding.

Main institutions conducting the research and examples of the projects:

ESTONIAN UNIVERSITY OF LIFE SCIENCES
Institute of Agricultural and Environmental Sciences, Polli Horticultural Research Centre.

They are mostly focused on the ways of growing crops, yet work little on the breeding as well.

Evaluation of the economically important parameters, phenotypic and genetic traits in blackcurrant cultivars, the elite selections and their pedigree in the Estonian breeding program

UNIVERSITY OF TARTU: FACULTY OF SCIENCE AND TECHNOLOGY
Institute of Molecular and Cell Biology, Chair of Biophysics and Plant Physiology (4 „top research leaders"), Chair of genetics (1 „top research leaders").

At the university, there is a research on the plant molecular biology and the genetic research that is generally fundamental (e.g. how photosynthesis works), yet they may be very close to the high-tech applications: discovery of a gene for GMO production etc.

- Functional relations between the plant structure and the physiological activity (investigates the environmental and genetic controls and possibilities for the genetic modification of the fundamental relationships between the structure and the functional activity of the leaves and the whole plant)
- Alternative and cyclic electron transport: the regulation and the role in plant photosynthesis
- The role of AI-2 and Rcs, the two-component regulatory system in the regulatory network, controlling the virulence in the bacterial pathogen *Erwinia carotovora*

Institute of Technology, Environmental Technology, Plant biology (1 „top research leaders").

A gene that regulates the function of the plant stomata has been localized in the collaboration with the scientists from the University of Helsinki and University of California, San Diego (USA). This fundamental research may be used for the development of plants with the increased stress tolerance.

TALLINN UNIVERSITY OF TECHNOLOGY: FACULTY OF SCIENCE
TTU is close to the market: research on the tools and the methods to execute high-tech breeding (mainly MAS).

Department of Gene Technology (2 „top research leaders"):

- The department participates in the State Program of Plant Breeding for the Years 2009-2019, contributing to the cereal pre-breeding and to the implementation of methods for biotechnology (molecular diagnostics, marker-assistant-breeding, determination of DUS criteria).
- Research project: Molecular and tissue culture methods in plant breeding and plant analysis

JÕGEVA PLANT BREEDING INSTITUTE:
Departments: Cereals, Fodder Crops, Potatoes, Vegetables, Biochemistry and Plant Protection, Gene Bank, Seed Centre, Mooste Experimental Station, Sangaste Experimental Station. There is mostly applied research (producing seeds) that is focused on the traditional breeding.

7 ETIS database, Institution websites, interviews, http://www.sordiaretus.ee/?pid=1870&pageHeader=Thesis

Relations and the inheritance of the qualitative and the quantitative traits of yield, disease resistance and quality in the breeding of field crops for sustainable agriculture

ESTONIAN RESEARCH INSTITUTE OF AGRICULTURE
There is mostly fundamental research and applied research – use of biotechnology but medium use of high-tech (meristem cloning).

- Department of Plant Sciences (agricultural ecology, field crops, plant protection, grasslands) – traditional breeding
- Department of Plant Biotechnology EVIKA (meristemal cloning of plants, potato disease eradication, horticultural plants, in vitro preservation methods of plant genetic resources, gene bank)

The application of the plant biotechnology methods (meristem method, somaclonal variation, microcloning) to the research of potentially dangerous plant diseases and to the research of the long-term preservation of plant genetic resources

Summary

A potent short- to mid-term research and development opportunity in Estonia:

Strengths ■ Existing competences in the traditional breeding and in the plant molecular physiology, in genetics & virology (with existing „top research leaders"). ■ Very structured traditional plant breeding infrastructure ■ Trend towards increasing concentration to the farms in Estonian landscape and to the intensification of agriculture. ■ Emerging scientific expertise in the advance breeding techniques, chiefly in the molecular marker assisted selection (MAS).	**Weaknesses** ■ Lack of competences concerning GMOs (little and very limited academic research). ■ No private companies doing any active plant breeding or any research and development in the given domain. ■ Modest use of the advanced biotechnology techniques for the plant breeding (meristem cloning versus MAS) in the applied research.
Opportunities ■ High expectations held for GMOs, for more environment friendly and productive agriculture. ■ International pressure to the developing countries for food safety. ■ Development of the biofuels stimulates the government interest for more productive energy crops.	**Threats** ■ Problematic public acceptance of the GMOs and, furthermore, of all the forms of technologies for plant breeding in Europe. ■ Uncertain regulatory context, limiting investor confidence. ■ Existence of very large players with intense competition. ■ Remaining plant genomes to the sequence, limiting biotechnology techniques to certain species.

Conclusion of the Potential for Estonia

The traditional breeding in Estonia is established and structured by public institutes. Further knowledge and competences in the plant molecular biology, genetics and virology (including „top research leaders" know-how representing three research groups), providing some basis for the advanced biotechnologies for the plant breeding (MAS, GMO). Some links have been established with these competences and applied to the research (such as the participation of the TTU Gene Technology Group in the State Program of Plant Breeding for the Years 2009-2019) but they are generally very rarely translated into the products on the market.

Regarding the opportunities on the global market, the majority of the international agrobiotech players and the current inexistence of the Estonian players, lead to the envisagement that the early out-licensing of innovations (if any), or eventually providing the services, is the most probable business application for Estonia. Furthermore, it must not be forgotten that the regulatory context is very complex, refraining the investors in Europe.

Therefore plant breeding would not be considered as a first-line priority, but rather as a long-term opportunity.

1.1.2 Animal Breeding Technologies

Introduction[8]

Definition of the Field

Animal breeding regroups all the techniques aimed at producing animals with the desired characteristics. Animal breeding applies to the most widespread livestock species of the developed countries in bovines, porcine, poultry, ovine and fish. In the same way as in the plant breeding, animal breeding started with the crossing of chosen parents and the selection of the offspring, and has become more and more scientific with the development of the genetics and the genetic technologies. Advances in the animal reproductive medicine (such as in vitro fertilization) have also played an important role. Most important biotechnology techniques include: marker assisted selection, cloning and the production of the transgenic animals.

In marker assisted selection (MAS), DNA sequences or patterns that are located in or near genes affecting the phenotype (called quantitative trait loci: QTL) are used as markers to track whether the gene or the chromosome segment of interest is present in the individual. DNA tests have been developed, for example, to track the presence of genes involved in meat tenderness or to determine whether an animal may be resistant or susceptible to a particular disease (e.g. BSE (Mad Cow Disease) resistance in cattle or Scrapie resistance in sheep).

Regarding transgenic animals, transgenic laboratory animals such as mice have been on the market for years and, more recently, an ornamental fluorescent tropical zebra fish has reached the US market. But this is not the case in agriculture, where no transgenic livestock has yet been approved for marketing, though many are under the development, but mainly in the research institutes. The most sought traits are: fast growth, improved nutritional composition (for healthier food production) and resistance to disease. Environmental issues have also been addressed, in particular, the creation of transgenic pigs that produce less phosphorus in their waste. However, the greatest part of the transgenic animal research for the commercial use is in the field of human medicine, for the production of drugs (cf: bioprocessing chapter).

Examples of Products and Services

Cattle:

- GeneSTAR DNA test, for beef tenderness and marbling (enabling MAS breeding), is available since the March of 2009 by Pfizer Animal Health (Genetic Solutions Ptu. Ltd, Australia). New tests for disease resistance, superior feed conversion and higher meat yield should be developed;
- The use of bovine embryonic stem cells to generate sperm cells and, hence to improve the performance of IVF-based breeding programs (Monash Institute of Medical Research, Monash University, Australia);
- Transgenic cows, resistant to the mad-cow disease (the production of healthy prion protein-knockout cows was reported by Hematech, USA in 2006) and to the foot and mouth disease;
- Genetic engineering of the bovine mammary gland to alter the composition of milk (to decrease fat and to alter endogenous proteins, to resemble composition of human milk).

Poultry:

- The highest interest to the breeding industry is the resistance to disease (ascites) and the egg shell quality;
- Transgenic chicken resistant to the avian flu (Purdue University).

Fish:

- Breeding for the adaptation to specific conditions (e.g. cold water tolerance, prevention of the inbreeding within fish stocks, resistance to the existing and emerging pathogens);
- Increased productivity: e.g. faster growth and sexual maturity, feed efficiency (Norwegian Salmon Farming Industry was able to reduce its feed costs by more than US$230 million per year as a result of the national breeding program. Furthermore, the genetically improved salmon was reported to grow twice as fast as wild Atlantic Salmon);
- AquAdvantage™ Atlantic salmon is a transgenic salmon, capable of growing faster, but not larger than standard salmon bred under the same conditions. The perceived advantages are mainly for the environment, as the growth-enhanced salmon requires less food and produces less waste. US regulatory approval for its commercialization has been sought since 1999 (Aqua Bounty Technologies Inc., US);
- Anecdotally, and with no direct link to agricultural use, GloFish, a fluorescent tropical zebra fish, originally developed by the scientists at the National University of Singapore for environmental monitoring, is on the US market since late 2003 for a pet use (Yorktown Technologies, Austin, USA). Indeed, the U.S. Food and Drug Administration (FDA) determined not to formally regulate it, as it was considered not to pose any threat to the food supply.

8 *Advances in Food Biotechnology*, Frost & Sullivan 2007; *Marker-assisted selection, FAO 2007; The role of biotechnology in exploring and protecting agricultural genetic resources,* FAO 2006; FDA http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/default.htm

International Business Potential[9]

International Market Size and Growth

- European Union market of animal output in 2007 was €141.2 billion; Estonian market of animal output in 2007 was €294.47 million.
- Food and Agriculture Organization (FAO) has estimated that demand for meat will double by 2030 (with respect to 2000); over the same thirty-year period the demand for milk will more than double.

Trends and Developments

The growth of the animal breeding market is driven by the following trends:

- The importance of the sustainable food production in a world challenged by the global population growth. The main area of concern will be the food and nutritional security in the developing countries (leading to the research on food production systems, resistant to environmental conditions and pathogens, food with increased nutritional value).
- In the developed world, there will be a growing awareness of and consumer demand for a healthy and nutritious food (low-fat milk, high-protein meat, etc).
- The global trend towards the industrialization of the animal production process. New genomic technologies enabling faster and more efficient breeding (i.e. substantial reduction of the cost of genotyping has stimulated the interest in the large-scale applications of MAS, advances in the genetic & linkage mapping & the QTL studies).
- European interest and funding in this domain, e.g. European cooperation's supported: FABRE-TP (Farm Animal Breeding and Reproduction Technology Platform), EA-TP (European Aquaculture Technology Platform).

Time to Market

- Development of the new DNA tests, it is estimated to last from 1 to 3 years.
- No transgenic animal has yet received the market regulatory approval, which for the moment could be regarded as limiting. For example, US regulatory approval for the growth-enhanced salmon AquAdvantage™ Atlantic salmon has been sought for 10 years now. A large step has been taken with the issuing of the FDA guidance on regulating the genetically engineered animals in January 2009, but it is strict and imposes new applications for the products from transgenic animals to be submitted (approval can take up to 10 months). Not taking into account these uncertain regulatory aspects, development of the transgenic animals is estimated at mid-term (~ 10 years).

Important International Market Participants

- Numerous small actors are present in the biotechnological breeding. As the transgenic animal development is a growing market, research institutions remain as the main actors. In molecularly assisted selection, the market is more structured and large players, such as Pfizer Animal Health or Merial (Igenity), are involved with numerous smaller actors, who still mainly present DNA testing services.

Identified Bottlenecks

- The scientific-intensive domain requires large investments;
- Fear of the economic consequences on small farmers with the development of the intensive breeding and on the dwindling of agrobiodiversity (conservation of the animal genetic resources);
- Issues and the diverging views on the intellectual property rights linked with the animal genetic resources;
- In the case of MAS, challenges include the selection of the most appropriate methods and tools for MAS, among them many may not be available for analyzing and managing the enormous quantity of data produced. Furthermore, it has been observed that the overall impact of MAS in the multi trait breeding programs is smaller than expected from the single-trait approaches (one trait is often improved at the expense of the others, i.e. negative genetic correlation);
- For transgenic animals, slowness of the government to define the regulations and the fear that consumers will shun food from transgenic animals, are behind the modest interest of the corporations and investors.

9 EUROSTAT, http://epp.eurostat.ec.europa.eu/portal/page/portal/agriculture/data/main_tables;
The role of biotechnology in exploring and protecting agricultural genetic resources, FAO, 2006;
Marker-assisted selection, FAO, 2007; Biotech 2008, *Life Sciences: a 20/20 vision to 2020*, Burrill & Company, 2008;
Livestock Report 2006, Food and Agriculture Organization of the United Nations; EY internal experts

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation[10]

Existing products / services

Products and services on the Estonian market are mainly linked with traditional breeding or with the artificial insemination, including:

- Artificial insemination stations
- Import & export of the semen of the genetically improved breeds
- Semen and embryo banks of the Estonian breeds

Farming of animals in Estonia is largely dominated by dairy cows (56.7% of total animal output in 2007), followed by pigs (22.2% of total animal output in 2007).

Largest companies and description of their activities in the field

Endogenous:

- Livestock
  Animal breeding in Estonia is organized through co-operatives and privately owned breeding associations. In 2006, the Veterinary and Food Board had approved 10 animal breeding associations and societies. The largest of these is the Animal Breeders Association of Estonia, representing breeders from cattle, pig, sheep and goats, horses, poultry and fur farming organizations. The largest of these, Eesti Tõuloomakasvatajate Ühistu represents breeders of Estonian Holstein, Estonian Red, Estonian Native and beef cattle. The activities of the association include breeding, herdbook keeping, pedigree certificates, cattle evaluation, collection and sale of the breeding materials, artificial insemination and the advisory services, cattle shows and auctions, livestock purchase and sale.
- Fish
  The Estonian aquaculture sector is relatively small; in 2003, the total value of the farmed fish production was approximately US$1.4 million, with around 25 farms and 100 people employed. The main species produced are trout, carp and eel. Some of the well-equipped fish farms with modern equipment and technology exist (e.g. Põlula Fish Rearing Centre, Kalatalu Härjanurmes, AS Triton PR) but numerous small farms are not adapted to the conditions of EU. FjordFresh Holding AS has planned a new Fish Farm in Audru, in 2012. This will be a fish farm with fully integrated recycled water system and one of the world's largest on-land fish farms. Eggs or juveniles are imported from abroad, as there are no local brood stocks or breeding programs.

Supporting Research and Development for the Field[11]

The main research and development institution in animal breeding is the Estonian University of Life Sciences, Institute of Veterinary Medicine and Animal Sciences. This institute is leading the research on breeding and on the transgenic animals in partnership with national and foreign partners. It is also providing, in the domain, the training of higher education, including doctoral programs.

Genetic improvement of the dairy breeds, through "traditional" breeding:

- Research of the dairy breeds, as a part of investigation and innovation activities of Bio-competence Centre of Healthy Dairy Products, has led to an international patent application: "Cattle population, producing milk with modified coagulation properties and methods of making the same" (WO2008/017311A1 published in February 2008). The patented method includes, as an additional selection marker, a molecular marker ([kappa]-casein genotype).

Genetic mapping & breeding in aquaculture: Research is conducted in the dedicated Department of the Institute of Veterinary Medicine and Animal Sciences. Biotechnological research is mainly fundamental, though genetic mapping has the direct application in MAS.

- "Genetic diversity and sustainable management of genetic resources of farm animals and fish", "Molecular genetic studies of interspecies diversity in fish: implications for conservation and sustainable management"2004-2007.
- "Integration of genetic linkage mapping and experimental ecology approach to investigate the genetic basis of local adaptation in early life stages of Atlantic salmon" 2006-2009.

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10 Interviews; European and US patent office; Statistics Estonia; http://www.biotech.ee; http://www.estonianbiotech.com; http://mail.koda.ee/ektk/koda_eng.asp?view=list; http://www.baltinfo.ee/46

11 Interviews; ETIS database; Institution and company websites; European and US patent offices
FAO. © 2006-2009. National Aquaculture Sector Overview. Estonia. National Aquaculture Sector Overview Fact Sheets. Text by Paaver, T. In: FAO Fisheries and Aquaculture Department [online]. Rome. Updated 10 October 2005. http://www.fao.org/fishery/countrysector/naso_estonia/en

No research on MAS tools has been identified but the development of genotyping tests in this objective has been envisaged. The existing Estonian competences and economic activity in diagnostics, bioinformatics and reproductive medicine, provide a significant basis for this.

Reproductive medicine: 8 research projects on dairy herd fertility, involving Estonian University of Life Sciences, Institute of Veterinary Medicine and Animal Sciences, Competence Centre on Reproductive Biomedicine and Reproductive Biology, Bio-Competence Centre of Healthy Dairy Products, in partnership with Animal Breeders Association, DeLaval, large dairy farms (e.g. OÜ Estonia, Põlva POÜ, Torma POÜ) and foreign research institutes are on-going. They are concerned with the development of the fertility monitoring tests, reproductive pathologies and cloning technologies. For instance:

- Bull semen fertility tests, development of the laboratory test packages for the AI industry;
- Evaluation of the affectivity of automatic estrus detection systems;
- Development of the cytological tests for the diagnosis of uterine inflammatory conditions;
- Embryo transfer, in vitro embryo production, embryo viability testing.

More remotely, research that is being conducted on transgenic cows for the production of human therapeutic proteins in bovine milk (new research and development area, started in 2008) by the Estonian University of Life Sciences, Institute of Veterinary Medicine and Animal Sciences, the Competence Centre on Reproductive Biomedicine and Reproductive Biology and the Institute of Technology of the University of Tartu, is generating competences on the development of the transgenic animals that could be applied in the long term to agriculture.

Summary

A potent short- to mid-term research and development opportunity for Estonia:

Strengths ■ Important animal farming sector, mainly dairy cattle. ■ Existing and structured breeding organizations and local breeding programs linked with the academic world. ■ Existing research on biotechnological animal breeding, including transgenic animal creation (though it is not applied to agriculture, competences are generated in the development of transgenic livestock). ■ International cooperation: Cost Gemini (European network), University of Munich, University of Helsinki) ■ Two competence centres (Bio-Competence Centre of Healthy Dairy Products, Competence Centre on Reproductive Biomedicine and Reproductive Biology) ■ Large farms with the potential to partner in the research programs and invest in the new technologies. ■ Combination of diagnostics, genetics and bioinformatics competences with the potential for MAS tools development.	**Weaknesses** ■ Biotechnologies in animal breeding are a rather recent domain. ■ Need for the development of the research resources to reach a critical mass for the international competition. ■ To accelerate tech transfer there is a need for the involvement of a more private biotech structures. ■ No MAS applied research projects identified. ■ Small Estonian companies versus international players. ■ Lack of biotechnological products on the market. ■ A need to modernize at least a part of the aquaculture sector.
Opportunities ■ The increasing demand for the animal products, in particular, in the developing countries. ■ Important pressure on farmers to increase the productivity, while limiting the environmental impacts. ■ Developing concern for "healthy" food and agricultural environmental issues, both of which can be addressed through animal breeding. ■ Significant research is on-going worldwide, representing an active innovative domain. ■ Advances in animal genetics and genotyping are providing the necessary knowledge and tools to envisage new breeding options. ■ Technologies globally considered as essential and studied by international organizations, such as UN. ■ Some MAS tests already on the market.	**Threats** ■ Complex regulatory issues and public acceptance for the biotechnological methods. ■ Existing controversial issues on IP. ■ MAS is still in its scientific infancy and technical issues remain. ■ At an early stage, emerging market for the biotechnologies, some important players are already positioned. ■ No transgenic animals for agriculture on the market.

Conclusion on the Potential for Estonia

Animal breeding for improving the agricultural characteristics of the farm animals is an important business field, pushed by the concern for food security in the developing countries, the "healthy food" trend and the environmental concerns in the developed world, also the increasing consumption of animal products in the emerging countries. Advances in the animal genetics and genotyping have provided innovative knowledge and tools to envisage novel breeding options.

Biotechnology in the animal breeding is an emerging research field in Estonia, with existing research activity, including the tight relationship with breeder's associations, and with the competence centres. Traditional breeding and modern reproductive medicine (artificial insemination) are in place and ongoing. Regarding more biotechnological technologies, research is led on the diagnostic tests and cattle cloning (though the latter is not for agricultural purposes). Estonia's combination of the competences in diagnostics, genetics and bioinformatics will be strong support for the development of these technologies, especially MAS tools.

However, the lack of Estonian biotechnological products on the market (or out-licensed inventions) has been identified. Although, the field is globally still in its early phase, Estonia needs to build up competences in this domain to attain a critical mass for the international competition (with the possibility of focusing on precise strength area(s)). Therefore, the developing of the biotechnological products for animal breeding may be considered as a mid-term (5-10 years) opportunity, but it will require focused investments on some areas, preferably linked with existing strengths, such as genetics, diagnostics and reproductive medicine (e.g. fertility tests, MAS tools).

1.1.3 Functional Food Products

Introduction

Definition of the Field
Functional food or medicinal food is any fresh or processed food, claimed to have a health-promoting or disease-preventing property in addition to the basic function of supplying nutrients. The general category of functional food includes: processed food or foods fortified with a health-promoting additives, like "vitamin-enriched" products; fermented food with live cultures are considered as functional food with pro biotic benefits.

In other words, functional food and drink are everyday packaged food and beverage products that contain specific physiologically active components that provide health and wellbeing benefits in addition to the basic nutritional functions.

Nutraceutical, a portmanteau of nutrition and pharmaceutical, refers to the extracts of food claimed to have a medicinal effect on human health. Traditionally the nutraceutical was contained in a medicinal format, such as, a capsule, tablet or powder in a prescribed dose, although more modern nutraceuticals, such as probiotic drinks and yogurt are now found in ordinary supermarkets alongside with the normal everyday versions of the product. The modern term 'nutraceuticals' is nowadays interchangeable with the term 'functional food and drink'.

Functional foods are an emerging field in the science of food due to their increasing popularity among the health-conscious consumers.

Examples of Products and Services
Products and services among the functional food may be split according to their properties and resulting applications: the cognitive health, mood, the health of the heart, digestive health, immunity system (antioxidant), bone, joint and tooth and multi-faceted health foods. Functional food products also cover the food allergy and intolerance products, age and gender targeted food, oral beauty and nutria cosmetics. Among these products, the following have been particularly successful:

- Pro biotic and pre biotic are being offered in specific and in the broader range of product formats;
- Omega-3 DHA is typically the core ingredient for the proliferating lines of the brain nourishing food and beverage;
- Products rich in antioxidant ingredients and pro biotic, are used to boost the health of immune system;
- Reservation from red grape products is used as an antioxidant;
- Soluble dietary fibre products, such as psyllium seed husk are used for reducing hypercholesterolemia;
- Broccoli (sulforaphane) as a cancer preventative;
- Soy or clover (isoflavonoids) to improve arterial health.

International Business Potential

International Size and Growth of the Market[12]

- The global nutrition market reached US$228 billion in 2006. The US nutrition industry grew by 10% in a year and reached the US$85 billion level, its highest growth since 1998.
- The market size for France, Germany, Italy, Spain, Sweden, UK has reached US$7,189.7 million, in 2007.
- The ingredients' market was worth US$3.3 billion in 2006, 20% more than its value in 2005.
- Between 2002 and 2007, the functional food and drinks average European growth was 6.5% (including France, Germany, Italy, Spain, Sweden, UK) and the forecasts are estimating a slight decrease to 4.6%, between 2007 and 2012.

Table 3: Functional food and drink market value and growth.

$m	*2002*	*2007*	*2012*	*GAGR 2002-07*	*GAGR 2002-12*
France	637,2	807.9	980.4	4,9%	3,9%
Germany	1,497.9	1,982.5	2,524.8	5,8%	5,0%
Italy	768.2	1,138.1	1,525.2	8,2%	6,0%
Netherlands	230.5	285.9	346.2	4,4%	3,9%
Spain	449.3	641.1	813.7	7,4%	4,9%
Sweden	157.5	250.9	317.7	9,8%	4,8%
UK	1,667.9	2,103.3	2,533.0	4,7%	3,8%
US	18,104.1	27,230.5	36,653.0	8,5%	6,1%
Australia	516.0	657.7	840.8	5,0%	5,0%
China	9,593.5	12,491.5	16,162.2	5,4%	5,3%
Hong Kong	1,217.9	1,720.2	2,332.9	7,1%	6,3%
India	1,511.6	1,940.5	2,408.9	5,1%	4,4%
Japan	12,094.5	16,377.5	21,808.8	6,3%	5,9%
New Zealand	108.6	132.6	170.0	4,1%	5,1%
South Korea	1,647.2	2,581.0	3,365.8	9,4%	5,5%

**2012 is a forecast*
Source: Datamonitor: Next Generation Functional Food and Drinks: Opportunities in Personalized Nutrition (DMCM4650), 2008

Growing consumption of the functional food and drink reflects the demand for more personalized, targeted dietary solutions. It has been indicated that there is a growing demand for the personalized food and drink products that offer a more targeted health benefits. Therefore, majority of the traditional food companies see their greatest growth potential in the products with added health, beauty and anti-aging benefits.

Health and wellness are a mainstream, a cornerstone for the aging population's quest to maintain their youthfulness. Health awareness, wellness and fitness become more important as part of the lifestyles of consumers and therefore also dietary choices. New dietary and nutritional trends are emerging, such as personalized nutrition (and related sub-trends). This creates significant opportunities for functional food and beverage manufacturers, as consumers demonstrate a real desire and willingness to understand how they can eat more nutritiously or compensate the poor dietary habits.

Trends and Developments

- Dietary concerns become more specific and new dietary and nutritional trends are emerging. Accordingly, companies are figuring out ways in which to increasingly market food and drink on a health platform, and the trend is expected to continue to develop in the foreseeable future. Enhanced nutritional benefits are emerging as the main means of differentiating food and beverage brands.
- Large food and beverage companies are ramping up partnerships with the functional ingredients suppliers to identify, evaluate and bring innovative products to the market.
- Nestle has branded 13 functional ingredients, including pro-, pre-biotical calcium, omega-3s and fiber and plant sterols. These ingredients were worth US$3.3 billion in 2006, 20% more than their value in 2005.
- The growing reliance on food labeling information is symptomatic of both the general and specific health concerns. Regarding the latter, consumers are increasingly relying on the label information to make informed decisions about the nutritional profile of food and beverage products that matter most to them.
- Given the growth of aging populations, the escalating levels of obesity and associated lifestyle illnesses, the personalization trend offers manufacturers a significant growth opportunity to market the targeted food and drink products to a wide range of consumers. In recognition of this, it is likely that the

12 *Datamonitor: Next Generation Functional Food and Drinks: Opportunities in Personalized Nutrition (DMCM4650)*, Burrill & Co, 2008, Life Sciences: a 20/20 Vision to 2020

manufacturers will begin to meet the growing demand for the personalized food and drink products, which offer more targeted health benefits

- Personalized nutrition overlaps with a number of other food and beverage trends and themes. It is now evolving with complex genetics based on a nutritional science towards nutrigenomics.
- Nutritigenomics is geared towards understanding the response of the body to diets and food factors through various "omics" technologies such as transcriptomics, proteomics, and metabolomics.
- Nutrigenomics is an area at the cross of the bioinformatics, genetics and food subjects, requiring excellence in these three fields.

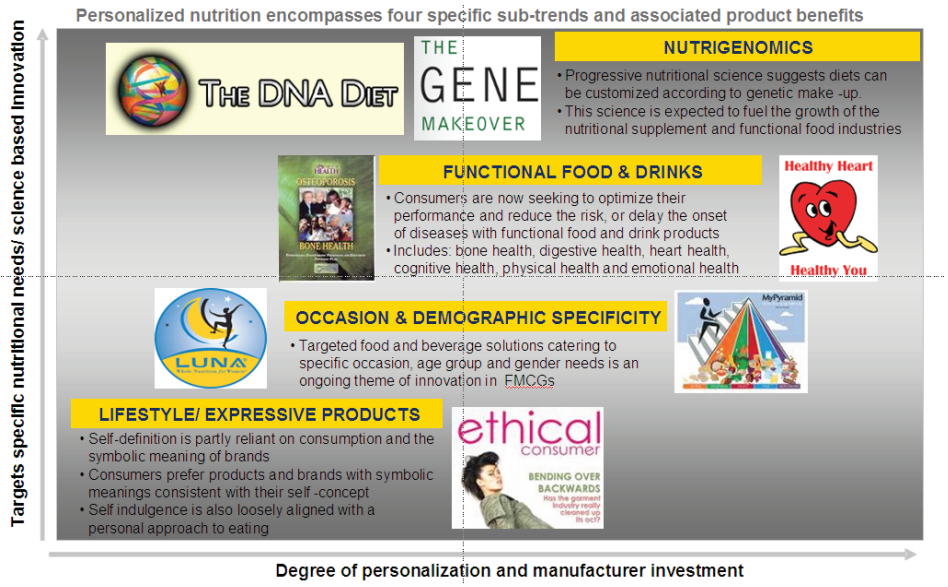

Figure 2: Functional food alternatives as a function of the degree of personalized investment
(Datamonitor: Next Generation Functional Food and Drinks: Opportunities in Personalized Nutrition (DMCM4650), 2008)

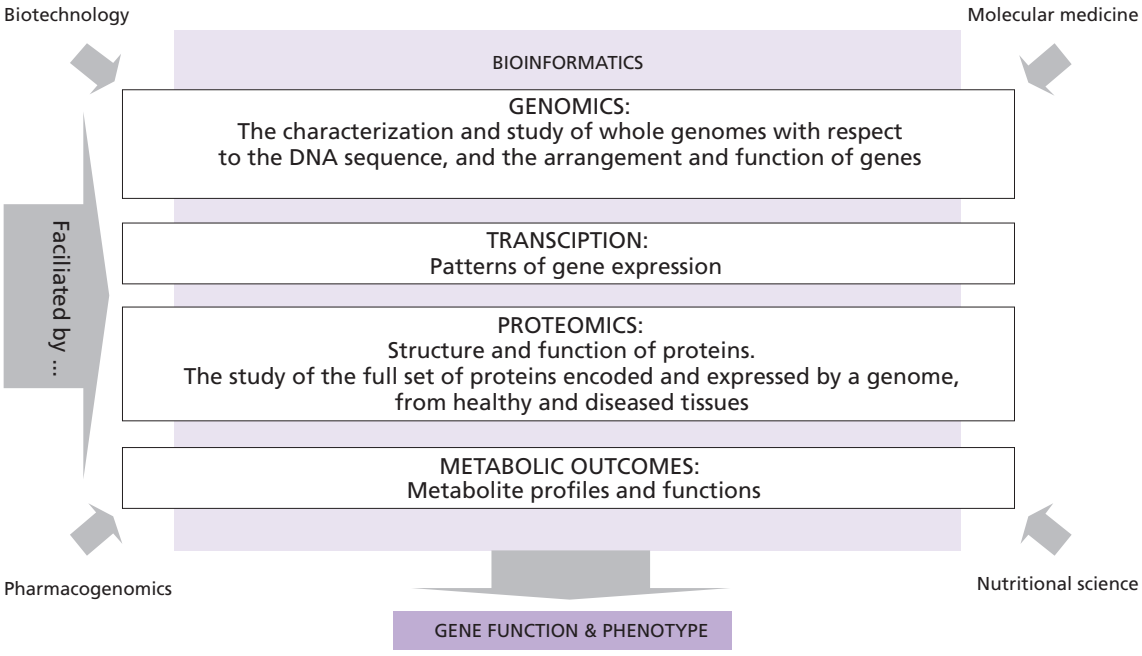

Figure 3: Nutrigenomics concepts.[13]

13 *Datamonitor: Next Generation Functional Food and Drinks: Opportunities in Personalized Nutrition (DMCM4650)*, 2008; Burrill & Co. Life Sciences: a 20/20 Vision to 2020

Time to Market[14]

- The development of a novel functional food product may be quite long with the go-to-market time around 5-7 years for a new active ingredient, if it is a cutting-edge innovation, the go-to-market time is around 3 years compared to a classical ingredient.
- The time to establish the proof of a concept for a preliminary efficacy, preliminary toxicity and for a basic formulation is about 24 months. These milestones are essential to secure the industrial property, the freedom to operate before licensing-out the product at a stage of development, and to be able to attract the industrials.

Important International Market Participants

- Top 10 health and wellness companies had an average revenue growth of 11.3% between 2006 and 2007. Among the Top 10 players, 6 companies had the revenue growth between 10% and 20% tear over year basis. The top 10 wellness companies considered are: Nestle, Groupe Danone, Dean Foods, Kraft Foods, Coca Cola, Pepsico, Hansen Natural, Hain Celestial Group, Unilever Group, Whole Food Market.
- Top 10 neutraceutical companies had an average revenue growth of about 13.2% per year in 2006-2007, including a growth up to 42% per year. The top 10 neutraceutical companies are: Hansen Natural, NBTY, Herbalife, Hain Celestial, Nu Skin Enterprises, Sunopta, Market Biosciences, Nutraceutical International, Schiff Nutrition International[15].

Identified Bottlenecks[16]

A couple of challenges still need to be taken into consideration by the functional food industry:

- Positive demonstration is compliant with the labeling on the packaging. Clinical demonstration is also necessary for the allegation leading to major investments associated with the risk.
- Today it is still difficult to identify the potential for receiving the economic return that corresponds to the added value.
- Industry trends are highly dependent on the regulatory constrains, which is the main instrument for new developments.
- Private insurance which is an important source of interest for the functional food trends is still often restricted to specific populations (i.e. children, elderly people), targeted pathology and not yet generalized to the whole population.

Assessment of Estonian Potential

Existing Production, Companies with the Potential for the Future Implementation[17]

The Estonian food industry is mainly based on the small companies with less than 50 employees.
The Estonian food industry market is mostly dominated by endogenous companies, with more than 10 companies, but there are also up to 10 exogenous companies that represent a clear critical industry mass for Estonia.

Existing products and services in the functional food industry

Existing businesses cover a number of different food products, including the dairy products, the production of cheese, production of frozen vegetables etc. Some concrete products represented on the functional food market in Estonia are:

- Pro biotic bacteria (e.g. ME-3) in dairy products
- Model for pro biotic evolution in the gastro-intestinal tract
- Functional jams
- Allergies and intolerance adapted products
- Pro biotic dog food

Examples of the Companies Involved in the Functional Food Field

- Tere AS
  Tere is a purchaser of crude milk, and the production and sale of dairy products, marketer of sauces, soy drinks and other non-milk-based products. They own a license for Lactobacillus fermentum ME-3 (ref. supporting research for the field)
- Bacterfield OÜ
  Focused on the pro biotic pet food, single line of functional dog food, numerous biotechnology projects, ranging from innovative pharmaceuticals to bacteria research and genetic applications.

14 Ernst & Young internal experts on Biotech
15 *Datamonitor: Next Generation Functional Food and Drinks: Opportunities in Personalized Nutrition (DMCM4650)*, 2008; Burrill & Co. Life Sciences: a 20/20 Vision to 2020
16 Ernst & Young internal experts
17 Espacenet, http://www.biotech.ee, http://www.tftak.org, http://www.estonianbiotech.com, http://www.baltcap.com

- NutriTech Baltics OÜ
  Nutritional and hypotonic drink for a specific population in the market. Focused on the sports drinks.
- S.A. Polar Sun Products OÜ
  Focused on the soy food production. Polar Sun Group has patented the process of the preparation of Soyappétit soy burger in Finland.
- Pro-Ekspert AS
  Pro-Ekspert is focused on the software development and the integration for the food industry.
- Balbiino AS
  Balbiino produces ice cream, cheese curds and the frozen vegetables line – Härmavili. Balbiino also emphasizes the product development, e.g. one of the yoghurt ice creams is produced from the company's own yoghurt.

Companies with the potential to be active in this industry
Bacterfield OÜ and Tere AS are more deeply involved in the functional food products and in the subject, from a research and development point of view, Tere AS being the company that has developed the ME-3 project.

Supporting the Research and Development of the Field
The intramural research and development expenditure in the manufacture of food products, beverage and tobacco industry represents less than 5% of all intramural research and development expenditure. Whereas applied research is the second largest intramural research and development expenditure with up to 60% of all research and development expenditure. Today, experimental development remains to be the main research and development expenditure sector in the food products industry. Nevertheless, local companies are not dealing enough with the research and development. The companies use two local competency centres for the research and development purposes (i.e. Competence centre for Food and Fermentation Technology, Bio-Competence Centre of Healthy Dairy). Hence, there is an indication of the interest in research and development, yet for the cost purposes they have limited the permanent teams inside the companies. The number of research and development in Estonia FTE in manufacture of food products, beverages and tobacco was around 10 in 1998, growing up to 42 in 2007.

There are no specialized Technology Transfer Offices in the field with industry international standards.

Estonia can rely on a good critical mass of institutions and universities working in the field of functional food subjects, and is able to support the industry in case the valorisation and the technology transfer are properly organized:

- Two universities extensively focus on the area, e.g. Tallinn University of Technology: Institute of Food Technology (fermentation of food, cell metabolism, modelling of micro-organisms); the Estonian University of Life Sciences: Department of Food Science and Hygiene, Department of Nutrition and Animal Products Quality (Technology of Foodstuffs (microbiology and biotechnology of foodstuffs, processing and storage of horticultural, plant, meat, dairy and fish products, the quality and quality control of the foodstuffs, sensory of foodstuffs, technical processes of foodstuffs, functional food, biochemistry of the foodstuffs)); hygiene of foodstuffs (hygiene and control of animal foodstuffs, pathogenic microbes in animal foodstuffs, microbiology of foodstuffs, contaminants in animal foodstuffs, nutrition hygiene).
- Two local competency centres, e.g. Competence Center for Food and Fermentation Technology (advanced micro-organism cultivation technologies, system biology of micro-organisms, food stability, quality and healthiness, modelling human gastrointestinal tract), Bio-Competence Centre of Healthy Dairy (improvement of the qualities of milk as an input to dairy product production, development of probiotic milk-based products).

This critical mass of the academic research is reinforced by Estonian key opinion leaders on the international levels, such as (but not limited to): M. Mikelsaar, K. Zilmer, J. Harro, T. Paalme.

This critical mass of academic research has led to 5 patent families.

There is one single license acquired by the local company, Tere AS. This company has licensed Lactobacillus fermentum ME-3 for Baltic countries and some European countries. On the other hand, there are 5 patent families owned (partly or fully) by the industry. From company side, the only one represented is Bacterfield OÜ.

Estonia has a critical mass for research and development as seen from the patented and licensed aspects. All of them are supported by the academic research by the different universities. In the business field, there are also numerous projects sent for grants, by today 7 have been identified.

The two largest remaining problems with the R&D in functional food is of the limited:

- bridges between the academia and the industry, for instance the technology transfer centres dedicated to the functional food (or at least food and life sciences) topics, unable to properly develop the very proof of the concept that is required for the out-license by the industry, unable to file the patent applications according to the international standards, unable to secure the right level of business development activities to secure the license according to international standards;
- dedicated or food-specialized venture capitalists, used for developing such products at the international standards and are unable to effectively contribute to the company governance and to top the strategy management. Therefore, there is a great lack of investments in the functional food field and in the food processing in general.

However generalist venture capital exist in Estonia with a limited investment in the traditional (not risky) food industry:

- Baltics Small Equity Fund (BSEF): a generalist venture capital firm that invests in small and medium-sized enterprises in Estonia, Latvia, and Lithuania, including the Premia FFL, an importer, wholesale and retail distributor of frozen food products in Latvia. Investment up to US$400,000.
- BaltCap Private Equity Fund (BaltCap OÜ): a generalist private equity and venture capital investor in the Baltic States (Estonia, Latvia and Lithuania) since 1995. Investment in a wide range of companies including in the NutriTech involved in the manufacturing and distributing of sports drinks.

Education

From the educational point of view, a couple of dedicated schoolings are currently performed in Estonia, particularly for the basic knowledge of biotech applied for the functional food or food processing:

- Tallinn University of Technology proposes a Bachelor's Degree program in Food Engineering and Product Development, Master's Degree program in Food Engineering and Product Development;
- Kuressaare College of Tallinn University of Technology provides a study program on Small Business Management (useful for endogenous company support);
- Virumaa College of Tallinn University of Technology provides a study program on the Production Engineering and Entrepreneurship;
- Estonian University of Life Sciences provides some dedicated courses in food microbiology and processing;
- However, there is a lack of Master of Science and Ph.D. specific programs leading to a limited research and development workforce available to support the academic and the food industry research field.

Summary

A potent short- to mid-term research and development opportunity for Estonia:

Strengths	**Weaknesses**
■ A critical mass in the functional food and the food processing industry, both endogenous and exogenous to rely on the in-licensing opportunities and research and development. ■ A critical mass in the academic research and development, with 2 competence centres and 3 universities with specialized departments. ■ A couple of patent files: ■ Up to 5 patent families owned (partly or fully) by industry; ■ Up to 5 patent families filed by universities and academia; ■ A unique success story: the lactic bacterium Lactobacillus fermentum ME-3. ■ Highly qualified research and development workforce (publications in peer review journals). ■ A couple of KOL (3 to 4). ■ A critical mass of projects submitted for grants and funding.	■ Limited number of patent applications. ■ Lack of the dedicated Master of Science and PhD. specific programs. ■ Lack of dedicated life science/food-specialized venture capital. ■ Lack of investments in the functional food. ■ Lack of the structuring equipment available for the industry under the industrial standard conditions (contractual conditions, confidentiality, safety etc.). ■ Lack of specialized Tactical Technology Offices used to support food research and development projects.

Opportunities	Threats
■ A market size of the functional ingredient more than $3 billion. ■ A market growth of 20% for the functional ingredients and 5% for the functional food and drink. ■ Large food and beverage players are increasingly partnering with the suppliers of the functional ingredients to bring innovation to market. ■ A growing demand for personalized food and drink products. ■ An emerging nutritional trend towards the personalized nutrition.	■ Regulatory constraint is the main instrument to push the industry trends. ■ IP needs to be absolutely secure to be ready for the partnership with big-player industry. ■ Time to market can reach up to 7 years for a new active ingredient. ■ Industrial patent policy, new research and development projects, new endogenous company, innovation needs to be more greatly supported (financially) in Estonia to compete at the international level. ■ Technological developers and business developers need to be either hired at the international level or locally educated to develop this field sustainably.

Conclusion about the Potential for Estonia

Functional food business field and more generally the food industry do represent a real critical mass in Estonia, together with a huge growing field from the international point of view. This field clearly needs to be supported, so it may become a real short- and long-term sustainable industry area of Estonia with two objectives: the internal and locoregional markets, as well as exportations of the patented innovations through geographical license agreements with international players. Innovation needs to be supported, with a particular focus on the patent filing and prosecution, the collaborations between industry and academia.

There are already numerous research projects submitted by the different universities and a number of patents have been filed, therefore, using and enforcing a closer collaboration within the country between the specific companies in the industry and the public research and educational institutions that would potentially offer beneficial mid-term licensing opportunities in the country.

As a longer-term goal, the creation of more intense collaborations between bioinformatics and genetic teams, which are considered as very strong fields in Estonia, and food industry people may lead to the development of nutrigenomics research and development programs and finally to the cutting edge innovation at the international level.

1.1.4 Food Processing

Introduction

Definition of the Field

Food processing is the set of methods and techniques used to transform the raw ingredients into food or to transform food into the other forms for the consumption by humans or animals, either at home or by the food processing industry. Food processing typically takes clean, harvested crops or slaughtered and butchered animal products, and uses these to produce attractive, marketable and often long-life food products. Similar processes are used to produce animal feed. Extreme examples of the food processing include the delicate preparation of deadly fugu fish or preparing space food for the consumption under the zero gravity.

Enzymes or biocatalysts are defined as proteins that have the catalytic functions supporting the vital biochemical reactions. They are typically derived from plant, animal, or microbial sources.

The basis for enzyme technology is the genetic engineering. Enzymes are mainly used in food and feed production/processing.

Examples of Products and Services

- Processed food products may include the food and grain enzymes, such as, amylases for bread-making, lipases for the flavor development, proteases for the cheese making, pectinases for clarifying fruit juices.
- Food sectors are greatly using certain types of enzymes:
  - Bakery (i.e. amylases, proteases, lipoxygenase, lipase);
  - Dairy industry (i.e. proteases, lipase, catalase, lactase);
  - Beverage industry (i.e. amyloglycosidase, papain, pectinase).

- Other food sectors are also benefiting from these enzymes, such as starch and sugar conversion enzymes (i.e. amylases, glucoamylases), fruit and vegetable processing, nutritional and dietary supplements, meat and fish processing, fats and oils, confectionery.

International Business Potential

International Market Size and Growth[18]

- The global processed food sales, worldwide, were approximately US$3.2 trillion (2004/2005). The last three decades have seen a tremendous growth in the sales of the processed food – sales are about three-fourths of the total of the world food sales. But contrary to the initial expectations, this phenomenon has not led to the significant growth in the global trade – only 6% of the processed food sales are traded, compared with the16% of the major bulk agricultural commodities.
- Market sizes, as indicated by retail sales value (Figure 1), are much larger for the developed countries. The United States, the European Union, and Japan together account for over 60% of the total of the retail processed food sales in the world. However, market growth has generally been faster among the developing countries, particularly in the lower-middle-income countries, such as China, Morocco, the Philippines, and many Eastern European countries. The transitioning of the Eastern European countries, such as Bulgaria, Romania, and Ukraine experienced a double-digit growth in the retail sales of many food and beverage products during the late 1990s. While sales in these markets have stabilized, Asian markets have picked up the pace in the past few years, and the sales of the processed food products are expected to continue increasing significantly. Packaged food accounted for US$100 billion in 2005 in Eastern Europe.
- The developing countries are expected largely to account for future increases in the food demand, resulting from the increase in the population and in per capita food consumption. Annual growth rates of the retail sales of packaged food products in the developing countries range from 7% in upper-middle-income countries, to 28% in lower-middle-income countries, much higher than annual growth rates of 2 to 3% in the developed countries. The packaged food products market grew by 70% between 2004 and 2005 in Eastern Europe. In comparison, the Western European growth on the same market was 60% during the period.
- The enzyme global market trends include annual sales around US$1.6 billion, the annual growth of 10 to15% by value and 4 to 5% annually by value with the decreased margins for the commodity enzymes and the increased use of specialty enzymes. Within this market, food and grain processing and enzymes market corresponds to 45% of the market share[19].
- Food processing (baking, pasteurizing and canning) will see a shift toward the non-traditional food processing techniques, such as microwave and radio frequency (RF) processing, ohmic and inductive heating, high-pressure processing (HPP), pulsed electric fields (PEF), ultraviolet (UV) light, ultrasound, and pulsed x-rays processing.
- Poland has one of the most dynamic food processing industries in the Eastern Europe. The presence of the large number of enterprises involved in the processing of food products, availability of the domestic and imported raw material and the country's accession to EU have given a new dimension to the food processing business in Poland. During 2008, total revenue from the food processing industry was estimated around US$67.45 billion, which is anticipated to surpass US$100 billion by 2011[20].

Trends and Developments[21]

- There is a trend toward a combination of rising incomes in the major Russian and Ukrainian markets and the benefits of the EU membership for Poland, the Czech Republic and Hungary are expected to underpin Eastern Europe's position as the fastest growing region in packaged food between 2005 and 2010, with the forecast value growth of just over 32%. With the increasing consumer confidence, the Eastern European countries are expected to demand more sophisticated packaged foodstuffs, offering a greater convenience, such as the frozen processed food, the ready meals and the chilled processed food, and the health benefits, such as fortified, low-fat, and organic products.
- Pro biotic foods, such as yoghurts containing pro biotic are the fastest growing products in Europe. This trend is expected to continue due to the ongoing research focusing on increasing the viability of these cultures by encapsulation. With the increasing number of the novel technologies emerging, it is possible to exploit many sensitive cultures that hitherto have been difficult to propagate. Dairy companies are now researching ways to develop a new technology that may result in more robust and longer lasting pro biotic ingredients for a wide range of products.

18 *"Emerging food processing technologies", Frost & Sullivan, 2005; Advances Food -08*, Frost & Sullivan, 2008
Processed Food Market in Poland Outlook 2012", RNCOS.
19 *„Enzymes – Global Developments and Trends"*, Frost & Sullivan, 2008
20 *Processed Food Market in Poland Outlook 2012"*, RNCOS
21 *Food Safety_0606; Emerging Food Processing Technologies*, Frost & Sullivan, 2005

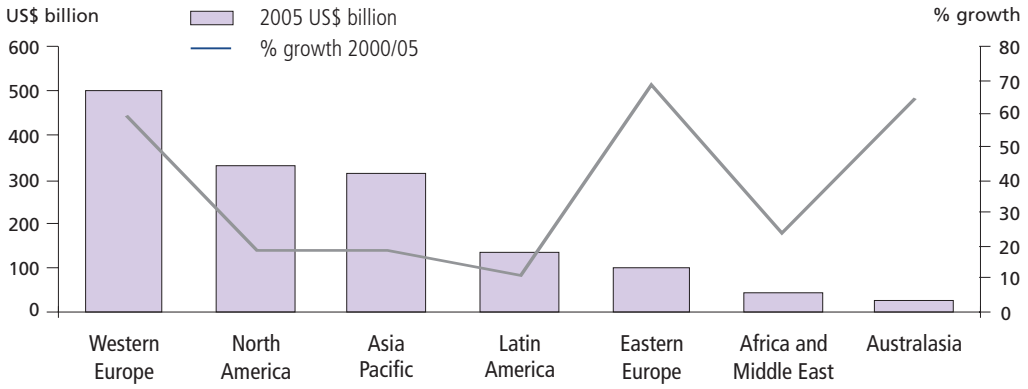

Figure 4: Global package food market size and growth

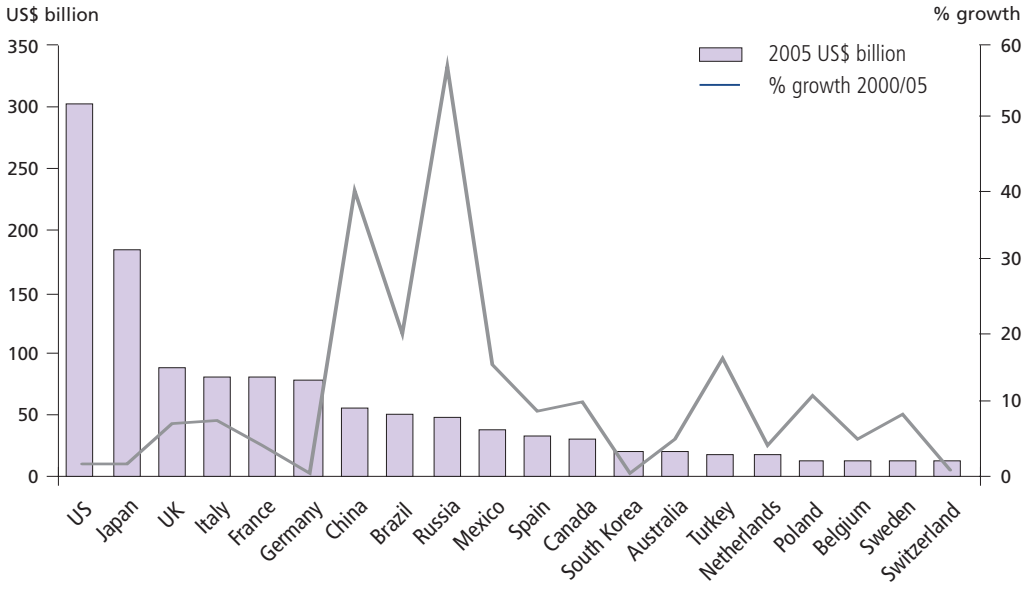

Figure 5: Global package food market size and growth

- A shift towards the new processing has been observed and may result in the increasing safety concerns (presence of high levels of possible carcinogen acrylamide found in baked and fried foods, or newly emerging food borne pathogens, resulting in the need to incorporate safety measures during processing, preparation, transportation, and storage of food to minimize the contamination risks), a need and a demand for a higher quality (growing demand for convenience and for the fresh products, such as ready-to-eat foods that have created a need to develop effective processing and preservation methods, better communication process, and cost-benefit ratio).
- Future trends for the research and development of the industrial enzymes include a genetic engineering to improve yields, strain improvement for higher yields and for a robust performance, development of the multi-step enzymatic processes, the whole cell conversion, using engineered micro-organisms, development of new enzymes to catalyze the reactions that are not currently possible with existing enzymes, improvement of the specialty of the enzyme products, reduction of the final prices of the enzymes.

Time to Market[22]

- The go-to-market time of 6 months to 2 years for innovative but traditional processed food
- However, it takes approximately 5-7 years to develop a new active ingredient within processed food (for instance: Activia with Danone)

Important International Market Participants

- The main companies focused on the food processing equipment are Zesto Food Equipment Manufacturing Inc. (Montreal), Ellie Corporation; Kal Kan Foods Inc., Sanyo Electric Co Ltd, Samsung Electronics Co. Ltd, General Mills Inc., Nestec S.A.; Stork Food and Dairy Systems B.V.

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- The main companies focused on the enzymes production are Novozymes with the enzymes for the dairy industry, Danisco with the enzymes for dairy industry, bakery enzymes, and culinary enzymes, DSM, Chr. Hansen, AB Enzymes.
- In 2008, AB Enzymes, Germany-based subsidiary of ABF ingredients, developed two new proteases – Veron HPP and Veron S50 – targeted at the bakery industry to reduce problems, such as browning and cracking. Novozymes, Netherlands, has launched Acrylaway, an asparaginase enzyme derived from Aspergillus oryzae that reduces the formation of acrylamide, a suspected carcinogen, during the production of baked or fried foods. In 2007, DSM launched CakeZyme that enhances the emulsifying properties of eggs, commonly used in baking to act as natural emulsifiers. The use of this enzyme could allow the manufacturers to reduce egg usage by 20% that can help cut down baking costs significantly. In 2007, Chr Hansen announced the expansion of its flavour production centre in Denmark to enhance its product range with the new production platform to include fermented butter flavours, compounded dairy flavours and the enzyme modified dairy flavour in addition to the production of cheese enzymes. In 2007, Novozymes launched Ultraflo Max, a beer filtration enzyme for the brewing industry. This enzyme offers increased capacity and reduced costs, regardless of the variation in the malt. In 2006, DSM Food Specialties launched a new pectinase for the red berry processing, known as the Rapidase Intense. This enzyme is expected to help the manufacturers achieve higher juice yields and stable colour. Some other food industry players include Nestle, Danone.

Identified Bottlenecks[23]

Challenges that are part of the processed food industry include:

- Alignment of economy and feasibility –For the successful applications of the emerging food processing technologies, it is essential that the interests of all these stakeholders be aligned. Not only should these technologies provide a better food quality, but they should also be at affordable costs.
- Improvement of standardization issues – One of the greatest challenges encountered in the development of novel food processing technologies is the lack of the standardization among the various component manufacturers for the equipment development.
- Emerging non-thermal technologies – There is a lack of communication parameters, and the measures between the food processors and the system developers have proven to be a major hurdle.
- There are also clearance problems from the Food Safety and Regulatory Bodies.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation

There are both endogenous (>10) companies and exogenous (>2) companies represented in the well-sized critical mass for a food processing market in Estonia. Represented companies are mostly involved in dairy, frozen vegetables, bread production, fish processed food, food monitoring and similar activities.

Examples of the companies involved in the food processing field

- Balbiino AS
  Balbiino is producing ice cream, cheese curds and frozen vegetables line – Härmavili. Balbiino also emphasizes the product development, e.g. one of the yoghurt ice creams is produced from the company's own yoghurt.
- Bioexpert AS
  The company is focused on the process monitoring, the developer and distributor of the fermentation software, distributor of the laboratory chemicals and equipment, and additives for the food production, consultation and analysis of the environmental projects.
- LDI Laser Diagnostic Instruments
  Focused on the environmental monitoring, food and pharmaceutical industries, prevention of counterfeit and fraud, process monitoring, pipeline leak detection. LDI Laser Diagnostic Instruments owns 3 patent families including 2 on drug detection. One of the patent titles is: Portable Device and Method for On-Site Detection and Quantification of Drugs.
- AS Leibur
  Large bread manufacturer. The number of different products which Leibur offers is nearly 50. The best known among them are undoubtedly rye breads Tallinna Peenleib, Toolse, Rukkipala and Madise, wheat bread Kirde and the product range Kuldne (Golden) for toasting.
- Paljassaare Kalatööstus
  Focused on the fish-processing industry. Paljassaare Kalatööstus exports around 90% of the output. Main products are breaded fish portions with sauces that are made from Hake (Merluccius Hubbsi and Gayi), Alaska Pollock (Theragra chalcogramma) or Hoki (Macruronus novaezelandiae).

23 *Emerging Food Processing Technologies*, Frost & Sullivan, 2005

- Dagotar
  Focused on the fishing industry, the processing and sale of fish and fish related food products.
- AS Kalev
  Kalev Chocolate Factory is the manufacturer of chocolate and sugar confectionery products, also the sale of chocolate, sugar and flour confectionery products. The main foreign markets are the Baltic States and Scandinavia, but also Russia.
- Puratos Estonia OÜ
  Focused on the bread and confectionary products, such as bread improvers, improvers for the frozen bakery products, o-tentic, enzymes, emulsifiers, canned fruits, cakes, sponge and chou mixes, various types of chocolates etc.

Among exogenous companies, some may be easily identified, e.g.

- Lallemand Inc
  Lallemand Inc is represented in Estonia through their subsidiary of the AS Salutaguse Yeast Factory. Mostly specialized in the development, production, and marketing of yeasts and bacteria.
- Tallinna Külmhoone AS
  Part of Amber Trust II S.C.A group. The core of the business lays in the production of ice-cream, sale of refrigerated foodstuff, sale of frozen foodstuff, cold storage.

Supporting Research and Development for the Field

The intramural research and development expenditure data is only available at the global level, taking into the consideration the food products, beverages and tobacco. This intramural research and development expenditure represents less than 5% of all the Estonian intramural research and development expenditure. Applied research is the second largest intramural research and development expenditure, with up to 60% of all research and development expenditure. Today, the experimental development remains to be the main research and development expenditure sector in the food products industry.

Similarly to the functional food business field (very similar), Estonia can rely on a good critical mass of institutions and universities working in the field of processed and packaged food subjects that are able to support the industry if valorisation and technology transfer are organized properly:

- Tallinn University of Technology and Estonian University of Life Sciences focus on the area.
- Estonian University of Life Sciences: Department of Food Science and Hygiene, Department of Nutrition and Animal Products Quality (Technology of foodstuffs, microbiology and biotechnology of foodstuffs, processing and storage of the horticultural, plant, meat, dairy and fish products, quality and quality control of the foodstuffs, censoring the foodstuffs, technical processes of the foodstuffs, the functional food, biochemistry of the foodstuffs; hygiene of foodstuffs, hygiene and the control of the animal foodstuffs, pathogenic microbes in the animal foodstuffs, microbiology of foodstuffs, contaminants in the animal foodstuffs, nutrition hygiene).
- Tallinn University of Technology: Institute of Food Technology (fermentation of food, cell metabolism, modelling of micro-organisms).
- Two local competency centres, e.g. Competence Center for Food and Fermentation Technology (advanced micro-organism cultivation technologies, system biology of the micro-organisms, food stability, quality and healthiness, modeling of the human gastrointestinal tract), Bio-Competence Centre of Healthy Dairy (improvement of the qualities of milk as an input to the dairy product production, development of the pro biotic milk-based products).

This critical mass of academic research is also reinforced by the same Estonian key opinion leaders at the international levels: M. Mikelsaar, K. Zilmer, J. Harro, T. Paalme.

No dedicated Technology Transfer Offices in the field.

There is not yet any other license acquired by the industry in this field, other than the ME-3 project, which is linked both to the processed and the functional food subject matter. However, there are two patents represented in the business field: the process for the preparation of a nutritive preparation based on the vegetable matter and the product prepared by the process and method of the production of biodegradable lactic acid polymers and the use of the lactic acid polymers produced using such a method, showing that the patent filing and industrial property strategy exists and needs to be encouraged in order to develop patent attorney skills and competences as well as support the cost of patent application for the academic sector once the invention is within the scope of the national priorities.

There is no dedicated venture capitalist for the food processing field, yet there are some examples of investments made by generalists, venture capital, such as Baltics Small Equity Fund (BSEF), BaltCap Private Equity Fund or Askembla Asset Management. NutriTech, Premia Tallinna Külmhoone and Tallegg have received investments by these companies.

Among institutional research initiatives, approximately 7 projects have been identified and are closely related to researches in the field with the quantifiable number of publications in the field (e.g. 10 publications on ETIS for "Food processing", 66 publications on ETIS for "yeast", 1 publication on ETIS for "Bread baking" etc). Among the project, the following have been identified:

- Research on the effects of the different raw materials and process parameters (bread fermentation, baking, packaging, storage) on the quality, taste and shelf life of the rye bread;
- Testing of the new sour dough starter strains, the fermentation and scalding technologies for the improved characteristics of the rye bread;
- Research on the production and downstream processes (biomass fractionation and purification) for the enhancing the biosynthesis of the interesting bioactive compound processes;
- Development of the "accelerostat cultivation method", enabling the study of cell physiology while changing the environmental conditions in the quasi steady state (the model organisms in use are *L. lactis, E. coli and S. cerevisiae*) as well as the corresponding data treatment and software development;
- Formation of the milk protein composition;
- Designing the fatty acids composition of milk.

The research initiatives can be followed up by companies for future business opportunities.

Education

From the point of view of training and education, a few options exist for receiving a basic biotechnical knowledge applied in the functional food or in the food processing, it may be done at Estonian University of Life Sciences at the "Veterinary Medicine and Food Science Department – FOOD TECHNOLOGY, HYGIENE AND QUALITY" as a doctorate program and at TTU with KATB02/09 Food Engineering and Product Development for Bachelor's level and KATM02/09 Food Engineering and Product Development for Master's Level.

Summary

A potential short- to mid-term research and development opportunity for Estonia:

Strengths	**Weaknesses**
■ Critical mass in the food processing industry to rely on, both endogenous and exogenous, opportunities for in-licensing and research and development. ■ A critical mass in the academic research and development with 2 competence centres and 3 universities with specialized departments. ■ Existing patent applications (> 3), inventions (3) ■ Highly qualified research and development workforce (publications in peer review journals). ■ A couple of Key Opinion Leaders (KOL) (3 to 4). ■ A critical mass of projects submitted for grants and funding.	■ Limited number of patents filed. ■ Lack of dedicated Master of Science and PhD specific programs. ■ Lack of dedicated life science / food-specialized VC. ■ Lack of investment in the food processing. ■ Lack of structuring equipment available for the industry under industrial standard conditions (contractual conditions, confidentiality, safety). ■ Lack of specialized Technical Tactic Offices used to support food processing research and development projects according to international industry standards.
Opportunities	**Threats**
■ Large and international industrial enzyme and processed food markets. ■ Two markets in the constant growth (>10%): +10-15% annually by volume and +4-5% annually by value for the industrial enzyme; +70% for the Eastern Europe packaged food between 2000 and 2005. ■ A major leap for the market of Eastern Europe (Poland is already a large and enthusiastic player). ■ Existing international industry in the field of enzymes production and food processing equipment, leading to many opportunities for short-term in-licensing, advanced development and commercialization. ■ A relatively short-term (6 months to 2 years) period for developing innovative but traditional processed food.	■ Existing international competition in the enzymes production industry, in the equipment industry and in the processed food industry. I■ ndustrial patent policy, new research and development projects, new endogenous companies, innovation needs to be much more supported (financially) in Estonia to compete at the international level. ■ Technological developers and business developers need to be hired either at international level or educated locally to sustainably develop this field.

Conclusion about the Potential for Estonia[24]

Processed and packaged food business field and, more generally, the food industry does represent a real critical mass in Estonia, together with a huge and growing market from the international point of view. This field clearly needs to be supported so it may become a real short- and mid-term sustainable Estonian industry area with two objectives: the internal and locoregional markets, as well as exportations of the patented innovations through the geographical license agreements or finished products with the international players. Innovation needs to be supported with a particular focus on the patent filing and prosecution, collaborations between the industry and academia.

There are already numerous research projects submitted by different universities and several patents have been filed, therefore using and enforcing a closer collaboration within the country, between the specific industry companies, public research and the educational institutions would potentially offer a beneficial mid-term licensing opportunities within the country. International collaborations should also be encouraged to participate in the development when the Estonian industrial property position has been secured on the per project basis.

Short- to mid-term opportunities for Estonia

- Immobilization of enzymes is a promising area of the food processing, allowing the development of continuous processes. Immobilized enzymes use only minuscule amounts of the required enzyme and may be easily separated from the reaction mixture. These enzymes exhibit greater thermal and operational stability. Immobilized biocatalyst is particularly suitable for the dairy industry (preparation of lactose-hydrolyzed milk and whey, using β-galactosidases).
- Enzymes for the dairy industry: chymosin (cheese production), proteases (cheese ripening), ligases (cheese ripening and cheese flavor production) and lactases (increases digestibility and sweetness in the dairy products, such as milk, yoghurt and ice cream). Pro biotic processing relies mainly on the probiotic encapsulation to offer a protection during the processing and storage to probiotic. This is applicable to biscuits, vegetables. For instance, Laval University in Quebec (Canada) has developed such technology.

Among the most promising emerging food processing technologies:

- HPP (high pressure-temperature processing): little effect on the food products but is lethal to yeasts, molds and vegetative bacteria. For instance Avure Technologies has developed such systems.
- PEF (pulse electric fields): increasing the shelf life with minimum changes in the nutritional and sensory quality of food (microbial and enzymatic inactivation tool). For instance, Stork Food Systems in the Netherlands has developed such systems (patent US 6,393,975). These technologies are associated with high investment and operating costs, limiting the return on the investment to a lengthy payback time. Regarding chocolates and drying fruit (Kalev being an Estonian chocolate factory), newer applications of the microwave technology should offer a uniform drying in a short time, while preserving flavours and texture.
- In a second step, the pulsed light treatment may provide a novel way to reduce micro-organism on the surface of meat, shellfish and bakery products. Other technologies, such as oscillating magnetic field, ohmic and inductive heating would need some more research and development before they get commercialized.

1.1.5 Food Diagnostics and Safety

Introduction

Definition of the Field

As known, food can transmit diseases from a person to person, it may also serve as a growth medium for bacteria that can cause food poisoning. Therefore, food safety has grown into an important business area. Food safety is a scientific discipline describing the handling, preparation, and storage of food in the ways that prevent food borne illnesses. It includes a number of routines that should be followed to avoid potentially severe health hazards.

Food safety has developed differently in the developed and less developed countries. In the developed countries, there are intricate standards for the food preparation, whereas in lesser-developed countries the main issue is simply the availability of adequate safe water, which is usually a critical issue.

24 *Emerging Food Processing Technologies*, Frost & Sullivan, 2005

Examples of Products and Services

- Traditional food testing solutions are mostly based on the classical biochemical tests that take a couple of days.
- Among the technological alternatives to the reference methods available in industrial monitoring, polymerase chain reaction (PCR) is a powerful tool for ensuring a fast specific answer in one day.
- Latest diagnostic food products under development are mainly the biosensors detection systems, including bio-chips or lab-on-chips targeting particular pathogens (*Listeria, Salmonella*) or quality indicators (*aerobic bacteria, anaerobic bacteria, bacillus, lactobacillus*). Recent solutions are focused on the ultrasensitive rapid detection systems of the pathogens.

International Business Potential

International Market Size and Growth[25]

- Food contamination refers to the presence or introduction of one or more contaminants in the food. The contaminants may either be biological agents (micro-organisms), chemical agents (pesticides and other chemicals) or other foreign objects, which have the ability to affect the safety and integrity of the food products and adversely affect health.
- The ingestion of contaminated food causes food poisoning or a food borne illness. Additionally, contamination may also occur due to the improper food preparation, handling, and storage practices, therefore, it is essential to maintain good hygiene practices prior to, after, and during the preparation of food to eliminate or at least reduce the chances of contracting an illness. The process involved in the monitoring of food to ascertain that it is devoid of contamination, is termed as food safety.
- Rising concerns over the food and water safety worldwide continue to increase the need for testing contaminants, thereby generating a strong demand for the agricultural and environmental diagnostics.
- The global agricultural and environmental diagnostics market is expected to reach US$2.4 billion by 2012, as stated by the Global Industry Analysts, Inc.
- Europe is the largest market for the agricultural and environmental diagnostics, with revenues estimated to have reached US$623 million in 2008. The fastest growing segment is the microbiology testing market, which also represents the largest market.
- Recent testing techniques involve the immunoassay technologies and rapid tests that replaced the traditional wet chemistry, bacterial culturing, and chromatographic analysis. Initially, testing was implemented on the dairy products for detecting anti-biotic contaminants, while the recent focus has turned towards the soil and water contaminants, such as polychlorinated biphenyls (PCBs), dioxins, and on agricultural residues, including fungicides and pesticides.

Trends and Developments[26]

- One factor that is driving the food testing and analytical technology revolution is the increased consumption of fresh fruit and vegetables. Increasingly, both domestic and imported produce have been found to contain microbial pathogens, in part due to the irrigation with contaminated water supplies. Another growing concern is the contamination of the ready-to-eat meat with *Listeria* monocytogenes, a pathogen that proliferates at the refrigeration temperatures. In both of these cases, there is often no heat treatment for killing the pathogens immediately, prior to consumption. The need for pathogen testing in the processed foods, or raw foods that are cooked prior to consumption, is not as strong. The Hazard Analysis and Critical Control Point (HACCP) procedures that are in place for the processed foods help to assure their safety. In addition, the cooking of the foods prior to consumption kills most microbial pathogens. It is of utmost importance that food safety systems be based on an extremely strong scientific foundation.
- Another developing trend is the increased consumer pressure for more safety and more information, globalization, and compliance with the United Nations World Trade Organization (UNWTO), European Union (EU), and Japanese regulations for import and export control. This continues to drive the growth of the food safety market that enforces companies to enhance their capabilities in the field through increased diagnostic activities.

Time to market[27]

- The go-to-market time is estimated between 5 to 10 years to develop a new technology (real-time PCR (Q-PCR)) and use it at the industrial level (routinely in the production processes).

25 *"Agricultural and Environmental diagnostics: A Global Strategic Business Report"* published by Global Industry Analysts, Inc.
26 *Advances in Food Testing – Analytical Technologies_0906*; Frost & Sullivan
27 Ernst & Young internal experts on Biotech

Important International Market Participants

- Dominant global market participants include Agdia Inc, Biocontrol Systems Inc., Biomerieux SA, Biotrace International Plc, Charm Sciences, C-Qentec Diagnostics, Eurofins Scientific, IDEXX Laboratories, Inc, Neogen Corporation, R-Biopharm, Strategic diagnostics Inc, and VICAM among several others.
- Particularly strong market player in the elimination of bacteria in shellfish and shucking shellfish is the Innovateit Seafood Systems LLC.
- A couple of clusters have chosen to invest in the food industry, including food diagnostic as a key and structuring area of biotech and life-sciences: French Brittany Quebec, Medicon, Hungary.

Identified Bottlenecks[28]

- The food testing industry is facing a challenge with respect to reducing the cost of testing involved. The greatest restriction is that rapid methods are expensive and the quality-control (QC) costs are often under the pressure in businesses that are trying to maintain profitability in a competitive marketplace.
- Typically, the enrichment systems used for pathogen testing need to be developed to the level where the cross contamination can be minimized or ruled out completely. This is an important aspect that would determine the use of a system. When the enrichment techniques are used, companies need to have isolated testing labs.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation

There is a limited number, but significant for Estonia, of endogenous (>4) companies and one identified exogenous (>1) company that are involved in the food diagnostics business field. Estonian food diagnostic companies include activities, such as consultation and analysis of environmental projects, process monitoring, sensor and measurement instruments, pipeline leakage, providing diagnostic products and reagents for the microbiology diagnostics, distributing additives for the food production etc.

Existing products and services in diagnostics

The range of products or services that may be identified covers the detection system for antibiotic residues in milk, the detection tool for milk suitability for cheese production or yeast fermentation modelling and monitoring

Examples of companies involved in food diagnostics

The endogenous companies present a broad range of activities related to this business field, such as fermentation software distribution, diagnostic tests for straight or serological detection of microbes and of the produced toxins, rapid tests of the microbiology or even prevention of counterfeit and fraud.

The following companies are representatives of this food diagnostic business field:

- Bioexpert AS
  The company is focused on the process monitoring, developer and distributor of fermentation software, distributor of the laboratory chemicals and equipment, and additives for the food production, consultation and analysis of the environmental projects.

- LDI Laser Diagnostic Instruments
  The company is focused on the environmental monitoring, food and pharmaceutical industries, process monitoring, pipeline leak detection. LDI Laser Diagnostic Instruments owns 3 patent families including 2 on drug detection. One of its patents is related to a portable device and a method for on-site detection and quantification of drugs.
- HNK Analüüsitehnika OÜ
  HNK Analüüsitehnika is focused on the diagnostics and analysis with specialization also in molecular, cell biology and life science products sales. They also sell environmental pollution monitoring and diagnostics equipment, analysis techniques, laboratory equipment and accessories.
- Evikon MCI OÜ
  Evikon is a sensor and measurement control instrumentation company. Specialized in the design, manufacturing and marketing of the sensor based measurement and control instrumentations.

28 *Advances in Food Testing – Analytical Technologies 0906*

One exogenous company has been identified in this particular field:

- Labema Eesti
  Labema Eesti is a provider of the diagnostic products and reagents for microbiological laboratories. Clients include all the significant food control laboratories, clinical laboratories, research centers, universities, and food or other industries involved in the microbiological diagnostics. Specialized in importing, marketing and delivering quality products for microbiology and clinical diagnostics, Labema Eesti provides microbiology products from sampling to the identification of microbes, quality control products, anaerobic workstations of the newest technology, and diagnostic tests for straight or serological detection of microbes and of produced toxins, rapid tests of microbiology and clinical chemistry, rapid drug tests.

Supporting Research and Development for the Field

- There is no critical mass in this field regarding the industrial property with the exception of the LDI Laser Diagnostics Instruments, having 3 patent families including 2 on the molecule detection.
- There is a number of established scientists in the field, e.g. from University of Tartu, Tervisliku Piima Biotechnol etc.
- In recent years, three projects have been submitted in the field concerning the optical biosensor system for the detection of antibiotics in milk, a laser-based spectrophotometical method for the assessment of milk quality and a selection of pro biotics for bio-quality and anti-infection ability of the milk products.
- There is neither a specialized technology transfer office nor dedicated venture capital or the seed funding, inducing a lack of valorisation from the university of research institution down to the industry as well as a lack of financing for the newly created and endogenous company.

Education

There is an emerging critical mass of universities and institutions working in the field with dedicated departments including:

- Tallinn University of Technology with the Department of Chemical and Materials Technology, Food Processing;
- University of Tartu with the Institute of Molecular and Cell Biology, in particular Microbiology and Virology;
- Estonian University of Life Sciences with the department of Institute of Veterinary Medicine and Animal Sciences, Department of Nutrition and Animal Products Quality and Department of Food Science and Hygiene.

Summary

A potential short- to mid-term R&D opportunity for Estonia:

Strengths	**Weaknesses**
■ A rather limited number of companies (<5 for endogenous and 1 to 2 for exogenous) to rely on for in-licensing opportunities and research and development, however significant for Estonia. ■ A critical mass in academic research and development with 2 competence centres in food and 1 competence centre in nanotechnologies as well as universities with specialized departments. ■ A high quality research workforce with Key Opinion leader. ■ Several projects (milk, yeast) of significant interest.	■ There is a lack of the specific training. ■ There is a lack of specialized seed funding and venture capitalist firms. ■ There is a lack of investment in the food diagnostic. ■ There is a lack of structuring equipment for development purposes (e.g. micro-array platform). ■ There is a lack of collaborations between food and nanotechnologies researchers. ■ Limited number of profiles with double-competencies: physical and biological/biotech competencies absolutely necessary for biosensor and food diagnostic development. ■ A very limited number of industrial project submitted for grant (1 only).
Opportunities	**Threats**
■ Increasing safety concern of the population. ■ Growing consumption of fresh fruit and vegetables. ■ Growing consumption of the packaged food with pathogen proliferation associated risk. ■ Ready to in-license food diagnostic biochips, Lab-on-Chip, PCR or RT-PCR dedicated tests.	■ The food testing industry is facing a challenge with respect to reducing the cost of involved testing.

Conclusion about the Potential for Estonia[29]

The food diagnostic business field could be considered as a side-business field for the global food industry with an emerging local critical mass that could support the important processed and functional food business fields of Estonia. In addition, the critical mass that exists in Estonia around the diagnostic topic (biosensors technologies, software, genetic knowledge, supportive workforce) could be easily adapted to target both the healthcare diagnostic and the food diagnostic subjects.

In addition, there are a number of short-term business opportunities for Estonia to in-license or collaboration:

- PCR-based detection of the antibiotic resistance genes in meat (Department of Food Sciences and Institute of Microbiology and Biomedical Sciences, Università Politecnica delle Marche, Ancona, Italy): the extensive use of antibiotic resistance (AR) genes as a selection marker in the genetically modified organisms, in human and veterinary medicine, and in livestock, is a cause of a growing concern. The main safety concern relates to the escape or transfer of these AR genes to sensitive bacterial strains, when these genetically modified organisms are introduced into the environment. As an opportunity there could be a development of PCR-based detection to determine the presence of AR genes in chicken and pork meat.
- New Hygiene Monitoring System (Strategic Diagnostics Inc, a biotechnology company based in Newark, DE, USA): development of the immunological testing kits for a wide array of applications, in particular the LumitesterPD-10N/LuciPac W System, a hygiene-monitoring test for food and food prep surfaces.
- *Listeria* Capture Kit Launched for Food Safety Testing (Germany-based Profos AG): Contamination of the food products as a result of the pathogens is a very serious issue encountered by the food industry and *Listeria* monocytogenes is a well-known pathogen.
- Biosensor technologies and in particular under a Lab-on-Chip (LOC) format for onsite detection.
- Detection of the food contamination (*E. coli*, *Salmonella*, *Listeria*).
- Real-time PCR (polymerase chain reaction) for detection of *Salmonella enteritidis* in poultry for meat and eggs (National Salmonella Reference Laboratory, Diedersdorfer Weg, Berlin, Germany): a robust real-time PCR for the specific detection of SE in chicken carcass rinses and consumption of eggs.
- DNA markers diagnostic test for the beef industry (Genetic Solutions Pty. Ltd., a Brisbane-based genetic information company): Tenderness has been demonstrated as most important palatability attribute of beef. Recent technological improvements have played a major role in ensuring the effective segregation of carcasses into the tenderness categories. The company offers the food industry innovative testing systems, required to improve the predictability and control in the food production chain. Further, there have been developed technologies for the product identification, validation, traceability, and the quality enhancement. Focusing on the beef industry, Genetic Solutions has developed DNA tests for beef tenderness and marbling that also could be considered as an opportunity.

1.2 Industry 2: Wood Processing and Pulping[30]

In 2007, the manufacture of wood and wood products represented 15.8% of all manufacturing activities of Estonia. The manufacture of pulp and paper and paper products represented an additional 2.5%, which is much higher than the EU's mean 8% of manufacturing industries represented by the forest-based and related industries. More than half of the land of Estonia is covered by forests, representing an exceptional reservoir of wood resources.

Although forestry is mostly a very traditional industry, there are several potential application domains in the industry for biotechnology to increase productivity, open new markets and limit the environmental impact.

Biotechnology can be used for:

- Selecting/developing improved tree species through MAS or GMOs *(see "plant breeding" business field)*
- To monitor forest development and pathologies
- To characterize wood fibres and to better assess wood quality (i.e. through immuno-profiling) for forestry planning and wood allocation
- To limit the environmental impact and bring new properties to pulp and paper through the use of enzymes in the pulp and paper industry *(see business field below)*
- To limit the environmental impact of the forestry industries through the biological waste treatment plants
- To produce energy from the cellulosic biomass (wood and waste of forestry industries) *(see "bioenergy" business field)*

29 E&Y internal experts; *Advances in Food biotechnology*, Frost, 2008
30 Statistics Estonia; European Commission: http://ec.europa.eu/enterprise/forest_based/index_en.html; EY internal experts

- To produce chemicals from biomass (wood and waste of the forestry industries) *(see "biobased chemicals" business field)*
- To produce high-tech products exploiting wood fibre properties at a cellular and molecular level (conductive materials, high-resistance composites)

The figure 6 illustrates the potential application domains of biotechnology in the forest industry.

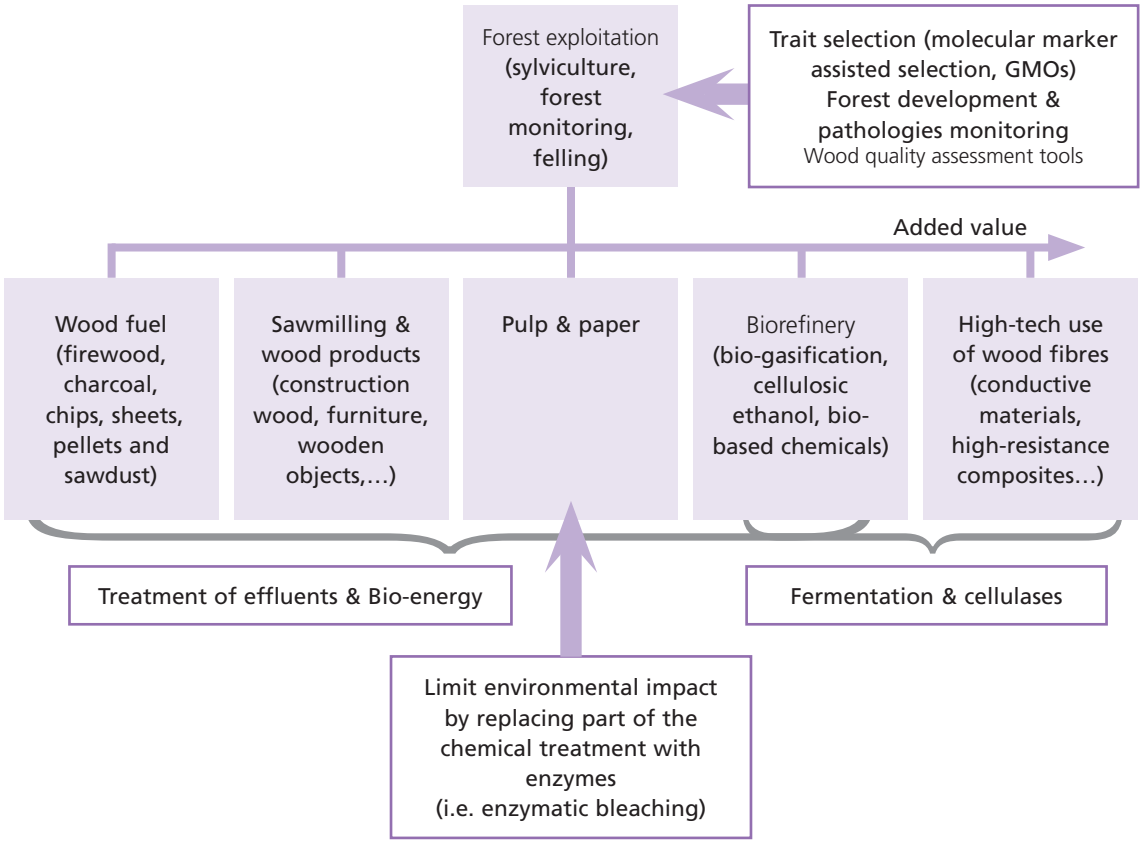


Figure 6: Potential application domains of biotechnology in the forestry industry

From the global perspective, these domains of application are not at the same maturity level. Biological waste treatment plants, bioenergy installations and enzymes in the pulp and paper industry are widespread applications, however, still very innovative domains. Biorefinery is still under development at a pilot stage, whereas high-tech use of wood fibres, forest development and the monitoring of pathologies, immuno-profiling for the wood quality assessment tools, are still at an early research phase.

In Estonia, only some biological waste treatment plants and biomass energy installations have been set up or are under research (for example: Estonian Cell AS, Horizon Paper Ltd). No other biotechnology projects have been identified, even at a research phase.

However, it is important to note that wood is an important feedstock for the potential biotechnology business fields, such as bioenergy or biobased chemicals. In this sense, the existing industry and the available competences and know-how in the forest management and exploitation in Estonia are the key success factors of the development of these fields.

1.2.1 Enzymes in Pulp and Paper Industry

Introduction

Definition of the Field[31]

The pulp and paper industry traditionally uses mechanical and chemical processing for its various operations. In order to limit the environmental impact of the industry and bring new properties to pulp and paper, the chemical treatments are being increasingly substituted by the enzymatic treatments. Key activity of the enzymes is to modify the cellulose fibres and thus optimize the bleaching, refining, deinking and wastewater processes. For example, it is estimated that the use of enzymes in paper bleaching reduces:

- chlorine use by 10-15%
- energy use by 40%
- water use by 18%

Other advantages of using the enzymes include the improved brightness of paper, the improved strength characteristics, less linting and dusting, reduction in stickies. In addition, enzymes can be applied to both the virgin and recycled fibres.

Examples of Products and Services[32]

Main enzymes used in pulp and paper industry:

- Proteases (microbial control in the paper and pulp processing),
- Amylases (remove starch content in the pulp),
- Cellulases (improve paper strength properties through fibrillation, increase the Schopper-Riegler (SR) index, reduce vessel picking),
- Xylanases (increase the Schopper-Riegler (SR) index, remove xylan from the pulp, reduce chemicals in bleaching while allowing enhanced lignin extraction, better brightness, increase pulp strength and make it more beatable),
- Esterases (remove stickies present in recycled fibres),
- Lipases (remove or control the pitch).

Proteases are the most consumed enzymes in the pulp and paper industry, representing 63.6% of the total volumes consumed in Europe in 2006. Amylases and cellulases account for respectively 14.2% and 10.6%. Lipases, esterases and xylanases all together account for the remaining 11.6%.

Formulators are also able to provide a technology support, product development, enzyme application expertise and other services.

International Business Potential[33]

International Market Size and Growth

- The paper and pulp industry is considered as a vital part of the European economy. It comprises more than 1,280 pulp and paper mills and between 2003 and 2004generated an annual turnover of more than €400.0 billion.
- It is estimated that enzymes in paper and pulp industry generated revenues of €29.7 million in Europe in 2006. This figure is expected to reach €37.8 million in 2013 with a compound annual growth of around 3.5%. Although the market is considered to be mature, its growth rate is considered to increase.
- The price range for paper and pulp enzymes tends to vary with end-user applications. In 2006, the price range was between €2.0 per litre to €50.0 per litre, with an average market price of €3.3 per litre.

Trends and Developments

The paper and pulp enzymes market will develop in the coming years according to the following factors:

- As pulp and paper industry is one of the most chemical and water intensive processes, the governmental and European standards and regulations are pushing the consumption of the environmentally friendly solutions, such as, enzymes.
- Due to the rising energy costs, mechanical pulp production processes, which are extremely energy intensive, are losing credibility. Mechanical pulp producers are therefore exploring the use of enzymes to reduce specific energy consumption required in the thermo-mechanical pulps refining.

31 *New Biotech Tools for a Cleaner Environment, Bio* (Biotechnology Industry Organization), 2002
European Markets for Enzymes in Industrial Application, Frost & Sullivan, 2007
32 *European Markets for Enzymes in Industrial Application*, Frost & Sullivan, 2007
33 *European Markets for Enzymes in Industrial Application*, Frost & Sullivan, 2007

- Increasing pressure to reduce the production costs without compromising pulp quality and yield is supporting the development of new technologies.
- As paper pulp components are biological materials (lignin, cellulose, hemicellulose), enzymes demonstrate a more beneficial effect on these components' properties than the chemical-based processes. Hence, new technologies for the pulp and paper manufacturing being developed currently are inherently enzyme based.

Important International Market Participants
The pulp and paper enzymes market is highly competitive as it is very concentrated; 75% of the market is controlled by the top three competitors. These prominent manufacturers are:

- Novozymes (40.5% market share in Europe in 2006)
- Genencore (22.5% market share in Europe in 2006)
- AB Enzymes (12% market share in Europe in 2006)

They supply to the formulators to a great extent rather than dealing directly with the market (with the exception of Novozymes). Formulators, for example the Buckman laboratories or Enzymatic Deinking Technologies (EDT), account for the remaining 25%of the market share.

Identified Bottlenecks
The following factors have been identified as restraints in the market:

- The enzymes used in the paper and pulp applications are considered to be expensive compared with the traditional chemicals.
- Stringent regulations and directives are likely to result in the increase of the number of closure of inefficient manufacturing facilities in Europe. This increase is such that it is expected to have a negative impact on the market potential for the paper and pulp enzyme solution. Furthermore, this may further intensify competition within the market and may result in the price-based competition.

Assessment of Estonian Potential[34]

Existing Production and Companies with the Potential for Future Implementation
No pulp and paper enzyme products or services have been identified on the Estonian market, but there are some companies identified with the potential for future implementation:

Two types of companies are concerned:

- Pulp and paper mills that could integrate pulp and paper enzymes in their processes – Estonian pulp and paper industry is limited to three actors:
  - Räpina Paper Mill – recycled paper production plant from the scrap paper
  - Horizon Pulp & Paper – unbleached kraft paper mill (acquired in 1995 by the Singaporean Tolaram Group)
  - Estonian Cell (owned by Heinzel Group from Austria, Larvik Cell from Norway and European Bank for Reconstruction and Development) – high-quality Bleached- Chemi- Thermo- Mecanical aspen pulp (BCTMP) (modern, more environment friendly process)
- Chemical suppliers that could add this type of the enzymes to their product portfolio – however, due to the fact that there exist only two potential clients, the commercial viability of this should be further evaluated (the 3 pulp mills could be directly supplied by European leaders).

Supporting Research and Development for the Field
No research and development on the pulp and paper enzymes has been identified in private or public structures. However, all paper mills are leading projects in order to diminish their environmental impact, illustrating their interest for environmentally friendly solutions. The strong government and European support, as well as the deterring environmental taxes are also the driving forces.

34 Interviews; ETIS database; European & US patent office

Summary

A potential short- to mid-term R&D opportunity for Estonia:

Strengths ■ Strong forestry industry. ■ Important forest resources. ■ Existing competences in the forest management and exploitation. ■ Existing pulp and paper industry for 300 years. ■ Awareness of the pulp and paper industry effect on the environmental issues and existing research and development projects to limit their environmental impact.	**Weaknesses** ■ No identified related products or services on the market. ■ No identified research and development, basic or applied, in private or public sector. ■ Limited number of actors in Estonia (only 3 pulp and paper mills).
Opportunities ■ Strong government and European support as well as the deterring environmental taxes act as driving forces. ■ Existing industry established but still innovating and developing at international level ■ A broad range of available products with beneficial effects in limiting the environmental impacts, improving product quality and productivity.	**Threats** ■ General opinion that the enzymes are more expensive than traditional chemicals. ■ Important pressure on the pulp and paper industry that could lead to the closure of certain mills and a high price-based competition on the market.

Conclusion about the Potential for Estonia

No research and development on the enzymes for pulp and paper production processes has been identified in Estonia as basic or applied research, in private or in public sector. Additionally, the business field is dominated by 3 large leaders and the industry may be described as having a tight competition. Therefore, development of new research and enzymes does not seem a plausible short- or mid-term opportunity for Estonia. On the contrary, uptake of the commercialized pulp and paper enzymes by this industry may be considered as an interesting short-term opportunity. Indeed, they are beneficial in limiting the environmental impacts, improving the product quality and productivity. Furthermore, this would contribute to pulling forestry industry of Estonia into a more modern and higher added-value industry.

Other short-term in-licensing or commercialized opportunities identified for pulp and paper industries[35]:
Paper mills have been using the black liquor residue from pulp production for several applications ranging from energy production to chemical recovery and the biomaterial production. For example, lignin from liquor has been used to manufacture biopolymers for the use as binding and dispersion agents, emulsion stabilizers, and extrusion aids.

- Chemrec (SE) has developed a gasification technology for turning black liquors into biofuels as well as biomaterials.
- TRI (US) has equipped the Norampac Trenton pulp and paper mill (Ca) with its black liquor gasification system enabling the spent liquor to be processed to recover the chemicals to be reused, while at the same time producing steam for the mill.

35 Company websites and publications

1.3 Industry 3: Chemical Industry

1.3.1 Bio-based Chemicals

Introduction

Definition of the Field[36]
Industrial biotechnology is the use of biological organisms (such as yeast, bacteria, molds etc.) or sub-cellular parts of those (e.g. engineered enzymes) to enable or improve the industrial processes, primarily in the chemical industry.

One part of the industrial biotechnology applied to the chemical industry is the bio-based chemicals. Indeed, biomass may be used as a feedstock, in replacement of oil and gas, to produce chemicals. Through biochemical processes (replacement of chemical synthesis with fermentation or biocatalysis), the carbohydrates (cellulose, hemicellulose and starch), fats, oils and lignin present in biomass may be transformed into bio-based chemicals that may then eventually be processed into high value-added chemicals.

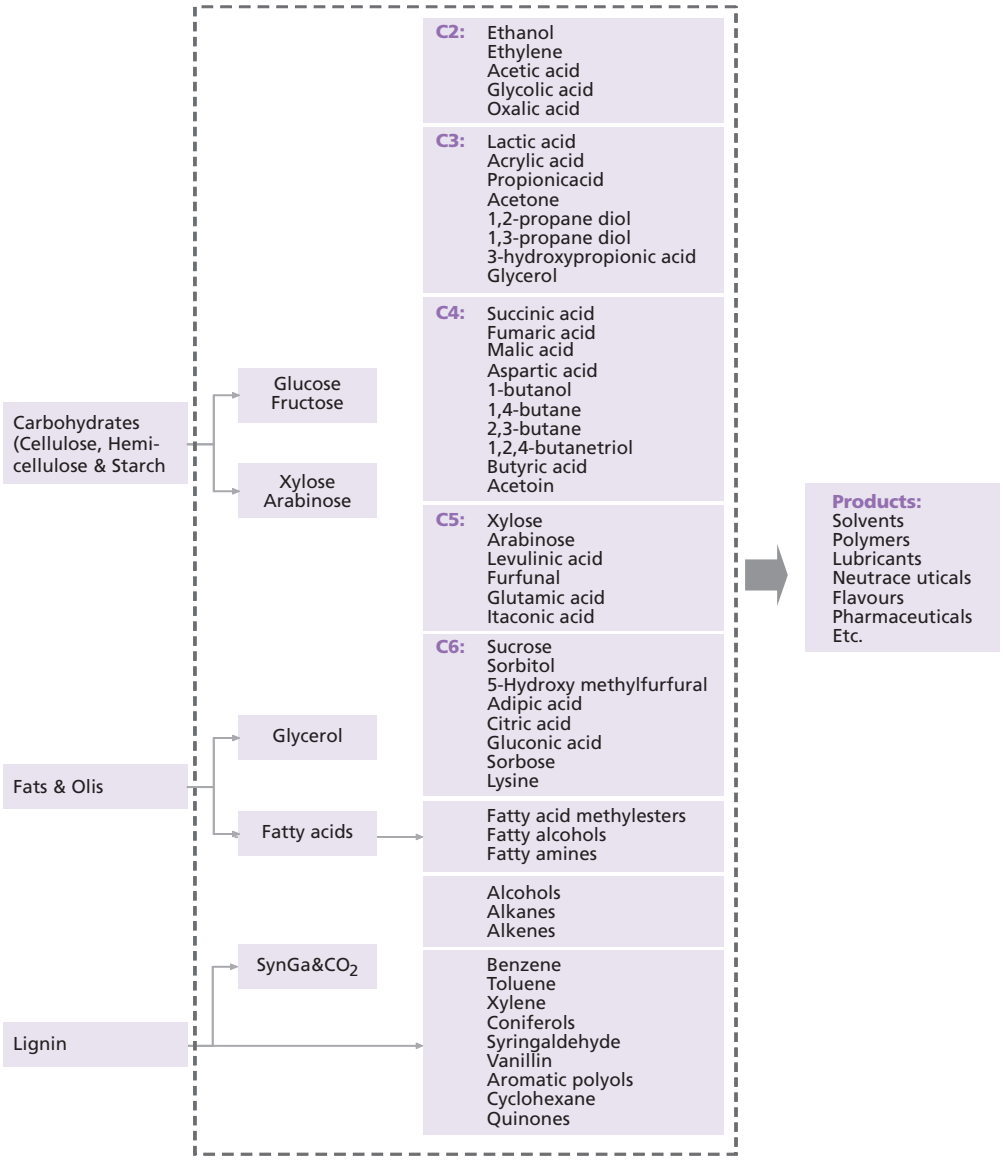


Figure 7: Chemicals and products that can be obtained through biochemical processing of biomass

36 *Engineering the Transition to the Bioeconomy*, Biotechnology Industry Organization, 2008
UK expertise for exploration of biomass-based platform chemicals. White paper by the FROPTOP group, 2007

First generation technologies mainly use easily accessible sugars (such as starch and sugarcane) as feedstock. However, new technologies are enabling production of bio-based chemicals from cellulosic biomass, such as the agricultural residues, forest products, municipal solid waste and herbaceous crops.

Examples of Products and Services[37]
Bio-based chemical products rely on either bio-based feedstock, fermentation, enzymatic conversion or a combination of these.

Product examples are solvents, polymers, lubricants, nutraceuticals or flavours.

The uses of bio-based chemical products are the following:
- Industrial – corrosion inhibitors, water treatment, specialty lubricants etc.
- Transportation – fuels, car seats, belt hoses etc.
- Textiles – carpets, fibres, fabrics etc.
- Safe food supply – packaging, fertilizers, appliances, vitamins etc.
- Environment – water chemicals, cleaners and detergents etc.
- Communication – plastics, computer casings, optical fibre coatings, liquid crystal displays, inks etc.
- Housing – paints, insulation, cements, varnishes, carpeting etc.
- Recreating – protective equipment, CD's, DVD's, camera and film etc.
- Health and hygiene – cosmetics, detergents, pharmaceuticals, aspirin etc.

Examples of the product opportunities in bio-based chemical industry:

From biopolymers to bioplastics:
- NatureWorks LLC has developed a biopolymer (polylactic acid PLA) Ingeo through fermentation of corn starch. First production plant started in 2002.
- Ingeo is currently present in a wide span of products – clothing, packaging materials, furnishings, coated papers etc.
- Complete life-cycle assessment of Ingeo showed that it requires 25-55% less fossil resources as the petrochemicals it replaces.
- DuPont and Tate & Lyle produce Sorona (1.3-propanediol PDO) via fermentation of corn starch. First production started in 2006.
- Metabolix and Archer Daniels Midland Company produce Mircel (Polyhydroxyalkanoates PHAs) via microorganisms fed with corn sugar. Production started in 2008.

International Business Potential

International Market Size and Growth[38]
International market size was approximately €65 billion in 2007.

Out of the €65 billion, traditional bio-based chemicals (natural rubber, essential oils etc.) form around €46 billion, chemicals by fermentation (bio polymers, organic and amino acids etc.) make up €14 billion and chemicals by enzymatic processes (pharmaceutical ingredients) constitute €5 billion.

Some market sizes by product groups in 2008:
- Pharmachemicals – €7.5 billion
- Citric acid – €2 billion
- Enzymes – €2 billion
- Glutamic acid – €1.5 billion
- Flavours and fragrances – €1.5 billion
- Lysine – €1 billion
- Vitamin C – €1 billion
- Vitamin B2 – € 0.3 billion

5% of the chemical sales in 2008 relied on biotechnology. In 2010 this figure may reach 10-20%.

37 *White Biotechnology: gateway to the future*, EuropaBio 2003
Advances in industrial biotechnology and biorefining, Biotechnology Industry Organization presentation, April 2008
38 *White Biotechnology*, McKinsey & Company, February 2009
Advances in industrial biotechnology and biorefining, Biotechnology Industry Organization presentation, April 2008

The market is predicted to increase by 35% from 2008 to 2012 and reach €88 billion in 2012. The split in 2012 is forecasted to be as follows:

- Traditional bio-based chemicals – €60 billion
- Chemicals by fermentation – €21 billion
- Chemicals by enzymatic processes – €7 billion

Largest growth comes from chemicals produced by fermentation with over 50% increase.

Trends and Developments[39]

Production of biochemicals is pushed forward by its advantages in comparison to the fossil-based technologies:

- Biomass feedstock (renewable resource, reduction of oil dependence)
- Increased efficiency (reduction of energy and water consumption during the process and reduced raw material consumption)
- Reduced CO_2 emissions
- Better degradability of co-products and effluents
- Reduced costs
- Higher safety
- Potential new properties of bio-based chemicals not found in petrochemicals

Recent technological advances allow transformation of biomass to the fermentable sugars through enzymes in an economical manner (the cost of the enzymes has dropped by more than 75% in the last 10 years).

Regulatory support across the globe helps to increase the use of bio-based chemicals. Governments have strongly pushed the use of renewable through mandates, subsidies and grants. For example, the European Commission 7th framework program for sustainable non-food products and processes (€ 700 million).

Time to Market[40]

Example of bio-based production of succinic acid project by Roquette Frères (starch and starch derivatives producer, France):

- In-licensing in December 2008 (genetically engineered E-Coli bacteria)
- Plant demonstration planned end of 2009
- Large-scale production by 2011.

Important International Market Participants

- Large multinational corporations from the chemical, food and biotechnology industries are operating in the bio-based chemical industry – BASF, Cargill, Dow, DuPont, Novozymes, Genencor, Roquette Frères, Evonik).
- Numerous joint ventures/partnerships have been observed between these large international groups and also smaller players (i.e. joint venture in 2007 between Cargill and Ashland for the development and production of the bio-based chemicals starting with high-grade propylene glycol from glycerin).
- The first biorefinery plants (plants that regroup several technological processes to optimize the utilization of the biomass feedstock in an integrated system) are appearing, though still mainly under experimental or pre-industrial project forms. It is believed that they will gradually emerge from biofuel projects and industry to the biorefining concepts including the production of bio-based chemicals (for example the pulp and paper industry).

Identified Bottlenecks[41]

- The competition with oil-based chemicals is mainly cost-driven and therefore the interest of investors is highly dependent on oil prices.
- The benefits of each bio-based chemical production route must be individually assessed, and according to the technology and the raw materials (type and production origin and conditions).
- Multi-product biorefineries still require development. However, in Europe, there are problems finding financial resources to build the biorefinery demonstration plants. As a consequence, companies setting up the biofuel facilities are holding back their expansion plans into biorefineries.
- Governments and the regulatory authorities will have to ascertain more economic power behind the significant environmental advantages than the industrial biotechnologies could provide.

39 *White Biotechnology: gateway to the future*, EuropaBio 2003; White Biotechnology, McKinsey & Company, February 2009
40 *Des produits chemiques verts en passe d'etre commercialises*, Rice University press release, December 2008
41 *White Biotechnology: gateway to the future*, EuropaBio 2003; *Europe Losing Battle for Biorefineries*, ICIS news, February 2009; *Biobased Products for Biomass Platforms*, National Renewable Energy Laboratory, 2004

- Threat from overseas countries (mainly BRIC – Brazil, Russia, India, China) that have lower production costs due to cheaper faster growing feedstock and labour.
- Commercialized technologies today deal mainly with the high sugar-content biomass (corn starch and sugarcane). Cellulose-derived technologies are still being developed in order to attain the required technological and the cost-efficient level.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation[42]
There are no companies in Estonia, that we are aware of, who currently produce bio-based chemicals.

Examples of companies with potential to be active in this industry:

Endogenous
AS Chemi-Pharm and AS Estko
- Currently they produce disinfection agent series for the medical institutions. They could potentially use the bio-based chemicals such as alkylpolyglucosides (APGs), instead of the oil-based materials.
- Research and development activities and competences on the bio-based chemicals not identified.

NordBioChem LLC (British and Estonian capital) – is developing a technological platform, enabling the production of the bio-based chemical intermediates (such as lactic acid, acrylic, propylene glycol, polypropylene, polyactate, polyacrylates) and their derived chemicals, including 3 high-volume bulk chemicals.
- An acid lactic production plant is planned in Hungary (in partnership with Nitrokemia), due in 2012. The plant will use 200 000 tons of wheat annually as feedstock.

Exogenous
Rhodia Acetow GmbH – produces cellulose acetate fibre that is used in the production of cigarette filters, has extended its patent application for its method for separating hemicelluloses from the biomass to Estonia as well (patent application pending).

Supporting Research and development for the Field
NordBioChem LLC:
- They have 10 published patents and 6 new applications, mainly around lactic acid production and derived biopolymers
- Mostly Russian inventors, except for the patent described below
- One patent is related to the work done in University of Tartu (published October 2007 and filed in 21 countries). Name: Thermophilic Microorganism Bacillus Coagulans Strain SIM-T DSM 10043 for the Production of L(+)- Lactate from Fermentable Sugars and Their Mixtures.

General research and development on the bio-based chemicals in Estonia:
- In 2006, 56.5 million EEK of intramural research and development activities expenditures is allocated to the enterprises in manufacturing of chemicals and chemical products. Most innovation expenditure is concentrated on the acquisition of machinery, equipment and software.
- Almost all intramural research and development expenditure in business sector were devoted to experimental development in 2006.
- In 2006 there were 203 research and development personnel (98 full-time employees, FTE) in the manufacturing of chemicals, chemical products, coke, refined petroleum products and nuclear fuel. This number grew to 225 people (105 FTEs) in 2007.
- Existing department at university or institution – no identified department dedicated to the production of chemicals from biomass. However, some departments like Department of Genetics and Environmental Technology Center in University of Tartu and Department of Polymeric Materials in Tallinn University of Technology have been involved in closely related projects. Furthermore, competences existing in microbiology, genomics, proteomics, as well as in chemistry and the material sciences support the development of the bio-based chemicals.
- No dedicated competence centres.
- No specialized Technology Transfer Offices.

42 www.biotech.ee; www.estonianbiotech.com; www.baltcap.com; pub.stat.ee; www.is.ut.ee/pls/ois/!tere.tulemast and mega.chem.ut.ee/%7Eaks; European Patent Office – Espacenet; Estonian Patent Office; Ministry of Transport and Telecommunications press release, July 2007; Estonian Research Portal; Ernts & Young interview and analysis; TTU Research Project Database; US PTO

Summary

Strengths Important microbiology and genetic research competences Existing research on the one bio-based chemical leading to a patent – shows the capacity of Estonian research to generate potential discoveries in this field. One existing company in Estonia with a strong patent portfolio. Large existing cellulosic resources in Estonia.	Weaknesses Lack of intramural research and development and applied research – most patents of NordBioChem are from Russian inventors. Stop on the Tartu bioplastics project has led to discouragement of research teams and set a disincentive precedent. Existing technologies are mainly based on corn and wheat starch as well as sugarcane bagasse – they are not grown excessively in Estonia.
Opportunities Very large and fast growing market. Applications in almost all industrial and manufacturing fields following the global trend of development of more environmentally friendly and efficient processes. Potential for the development of products with new properties opening new large fields of innovation. Large players investing significant amounts of money and willing to partner with smaller innovative players. Strong support from the agricultural sector to find new value-added markets for their products.	Threats Need for further technological developments to make cellulosic feedstock cost efficient. Current research emphasis only on bioethanol and biodiesel production. Existing players have an advantage over Estonia.

Conclusion about the Potential for Estonia

Bio-based chemicals are a very important and fast growing market globally, with attractive environmental advantages.

The research and development competences in Estonia concerning microbiology, genetics, bioinformatics and metagenomics are a valuable basis for the development of bio-based chemistry, and have already led to a patented technology.

Currently, no companies are marketing bio-based chemicals, but one company has a developed patent portfolio and is planning to enter the market in the nearest future.

Currently marketed technologies rely on starch and other easily accessible sugars which are not easily available in Estonia (competition with food applications of agricultural crops).

Important resources in forestry industry of Estonia have a high potential as feedstock, however technologies relying on cellulosic biomass are still in development phase.

In conclusion, bio-based chemicals have potential for Estonia but are not recommended as a top priority.

1.4 Industry 4: Environmental Technologies

1.4.1 Bioremediation

Introduction

Definition of the Field[43]
Bioremediation is a process that uses micro-organisms to reduce, eliminate, contain or transform the contaminants that are present in soils, sediments, water or air. The technologies are classified as:

In situ – treating contaminants on the site
- Biodegradation/biostimulation – adding various nutrients (like phosphorus, nitrogen or carbon) to stimulate naturally occurring bacteria in order to degrade organic contaminants
- Bioventing – supplying air and nutrient through wells to contaminated soil in order to stimulate indigenous bacteria
- Bioaugmentation – addition of microbial strains to enhance microbial populations
- Biosparging – injection of air under pressure below water table to increase groundwater oxygen concentrations

Ex situ – treating contaminants on another site
- Land farming – tilling the upper soil zone
- Composting – organic matters get recycled in an environment under aerobic conditions
- Biopiles – hybrid of land farming and composting
- Bioreactors – device that helps a biologically active environment to degrade contaminants by adding liquid or air

An emerging technology called phytoremediation uses plants to remove contaminants from soil and water. Phytoremediation is in particular well suited for very large field sites (where other methods are not as cost effective or practicable), for low concentration sites (as a polish treatment over a long period of time) and for sites where vegetation is used as a final cap and closure of the site. Phytoremediation techniques have been classified according to the fate of the contaminant:
- Phytoextraction or phytoaccumulation – Direct uptake and concentration into the plant tissue with subsequent removal of the plants
- Phytotransformation – Plant uptake and degradation of organic compounds
- Phytostabilization – Root exudates cause metal to precipitate and become less available
- Phytodegradation – Microbial degradation is enhanced in rhizosphere
- Rhizofiltration – Uptake of metals in plant roots
- Phytovolatilization – Selenium, mercury and volatile hydrocarbons are evapotranspirated by plants
- Vegetative cap – Rainwater is evapotranspirated by plants to prevent leaching contaminants from disposal sites.

Examples of Products and Services[44]
Business areas where generated pollution can be treated through bioremediation:
- Drycleaners and chemical manufacturing (contaminated by chlorinated solvents)
- Electrical manufacturing, power stations and timber treatments (contaminated by polychlorinated biphenyls)
- Oil storage, gas work sites, airports, paint manufacturing and port facilities (contaminated by BTEX)
- Agriculture, recreational areas, landfills and pesticide manufacturing (contaminated by pesticides)

Examples of products:
- Microbial strains for Bioaugmentation – examples are CL-Out and Petrox (produced by CL Solutions, USA). Petrox was developed for cleaning petroleum spills and CL-Out was developed for chlorinated organic solvent spills.
- Additives and nutrients to stimulate the existing micro-organisms (Biostimulation) – for example, the emulsified oil substrate (produced by EOS Remediation, USA) that is used to treat chlorinated solvents, energetic materials, oxidized heavy metals and radionuclides in groundwater.

43 Bioremediation. An Overview, M Vidali, 2001, IUPAC Pure Appl. Chem.,Vol 73, No 7 pages 1163-1172, 2001
44 Bioremediation. An Overview, M Vidali, 2001, IUPAC Pure Appl. Chem.,Vol 73, No 7 pages 1163-1172, 2001; Emerging Bioremediation Technologies, Frost & Sullivan, 2006; Biotech for toxic use reduction, Frost & Sullivan, 2008

Examples of services (usually coupled with product sales):
- Remediation contractor handles the complete contaminated soil and groundwater decontamination projects
- Consultancy – evaluation of the feasibility of bioremediation and choice of products and optimal modus operandi

International Business Potential[45]

International Market Size and Growth
No global market size number was found. In the US in 2003, the whole environmental industry was evaluated to be worth US$213 billion, US$7 to US$8 billion being dedicated to remediation specific services (of which bioremediation is only a limited part). It is difficult to estimate the costs for bioremediation processes, and therefore the market size, as they depend greatly on the contaminants, the soil type, site hydrogeology and water chemistry.

From the general point of view, the bioremediation processes are frequently less aggressive than physical and/or chemical methods, so that cost savings may be achieved even with the higher operation and maintenance (O&M) costs associated with the longer treatment times associated with bioremediation techniques.

Some examples of ranges of treatment costs are:
- Enhanced bioremediation (bioaugmentation and biostimulation): US$30 to US$100 per cubic meter of soil, US$40 to US$60 per litre of the residual fuel removed from an aquifer through nitrate enhanced treatment.
- Bioventing & Biosparging: US$10 to US$70 per cubic meter of soil.
- Bioreactor for water treatment: US$80 000 to US$85 000 to install a single unit with a protective cover and a surface area of 9 300 to 13 900 square meters.
- Phytoremediation : US$60 000 to US$100 000 for one acre of lead-contaminated soil to a depth of 50cm.
- As a comparison, excavating and land filling one acre of soil on 50cm costs US$400 000 to US$1 700 000.

It is considered that the bioventing and biostimulation types of enhanced bioremediation are cost effective choices for soil type treatments (from a unit cost point of view). For groundwater treatment, the biostimulation again is a cost effective alternative followed by wetland construction.

The technologies, which are most likely to see the highest increase in the next couple of years are Enhanced Bioremediation with some elements of Biosparging involved, as combined treatment approach and monitored natural attention as polishing steps towards the end. This is linked with the current growing concerns with chemicals, such as perchlorate, PCB's, and heavy metals. For example, bioremediation technologies, such as the ORC, HRC and HRC-X products of Regenesis have shown tremendous increase in the past year and continue to grow. Estimation of the dollar value for this specific technology alone is almost close to US$475 million for the current sites being monitored in the US over a period of three years. Arcadis with the "Molasses" technology for enhanced bioremediation as one of their main biological technology application reported a gross revenue of US$108 million for 2002. Considering the wide application of these two technologies, these revenues are likely to at least double in the next year. Also there is likely to be some increase in phytoremediation and the constructed wetland market. Also the demand for cost effective technologies influences increase in the in-situ technologies more than ex-situ treatment options, such as Bioslurry, Bioreactor or Biopile systems.

Trends and Developments[46]
Bioremediation techniques have shown tremendous growth since the first demonstration of micro-organisms' clean-up of oil spills in 1964. The acknowledged advantages of bioremediation are:
- Bioremediation is a natural process perceived by the public as an acceptable waste treatment process for contaminated material, such as soil. Microbes are able to degrade the contaminant increase in numbers, when the contaminant is present; when the contaminant is degraded, the biodegradative population declines.
- It is useful for the complete destruction of a wide variety of contaminants. Many compounds that are legally considered to be hazardous may be transformed to harmless products. This eliminates the chance for the future liability associated with the treatment and disposal of the contaminated material.

45 *US Bioremediation Markets*, Frost & Sullivan, 2003
46 Bioremediation. An Overview, M Vidali, 2001, IUPAC Pure Appl. Chem.,Vol 73, No 7 pages 1163-1172, 2001; US Bioremediation Market, Frost & Sullivan, 2003; EY internal experts

- The complete destruction of the target pollutants is possible through bioremediation.
- Bioremediation can often be carried out on site, often without causing a major disruption of normal activities. This also eliminates the need to transport the quantities of waste off site and the potential threats to human health and the environment that may arise during transportation.
- Bioremediation may prove less expensive than other technologies that are used for the clean-up of hazardous waste.

Market development is driven by the following factors:
- Regulatory requirements – including European, national and local requirements
- Competitive pricing – more often than not the bioremediation technologies can be found to be cost effective compared to other technologies.
- With application of bioremediation technologies there is a reduced or no risk of further toxic by-products being generated after treatment of the hazardous compounds, unlike the thermal or chemical treatment technologies.
- More public acceptance: for example bioremediation with plants – "Phytoremediation" – is aesthetically more pleasing. Also more recently, a research is being conducted to use hybrid plants with a greater phytoaccumulation or extraction or degradative capabilities, which may be a safer alternative to GEMS (genetically engineered micro-organisms). With GEMS the regulators are apprehensive about inability to contain the population distribution in nature which can be easily solved with plants by breeding sterile species.
- Multipurpose Bioremediation technologies – biological technologies with capabilities to remediate different types of contaminants and in varied matrix in comparison to chemical, physical or to the thermal technologies, will increase the demand for such technologies.

Time to Market[47]
- Time to market depends greatly on the type of technology and/or product. For example, it is estimated that it takes 2-3 years commercializing a biostimulation additive and/or nutrient product. On the other hand, isolating a microbial strain or mix may take 3 to 5 years.
- It may be noted that an important part of the time to market is devoted to obtaining regulatory approval at a project-based level (especially regarding strict performance criteria and post-treatment residues). As an example, earlier this year the EOS® bioremediation product took one year to obtain California's very strict regulatory approval for a specific groundwater treatment project.

Important International Market Participants[48]
Main market participants are environmental/engineering companies, consultants, equipment vendors and, as suppliers, chemical and nutrient producing companies and biological agent producing companies.

Bioremediation market is highly driven by the leading US companies, for example:
- Remediation and Natural Attenuation Services Inc. – founded in 1998 as a bioremediation consulting company.
- EOS Remediation LLC. – leading US based company with products available worldwide for in situ remediation.
- Regenesis – range of specialty soil and groundwater remediation products (enhanced aerobic and anaerobic bioremediation, bioaugmentation, chromium immobilization, chemical oxidation) and services (design, support, review and oversee in situ remediation projects).
- Terra Systems Inc. – they have been developing in situ bioremediation technology since 1980s.
- Oil Cleaning Bio-Products Ltd. – supplies a complete range of safe, effective and biodegradable absorbents, bacterial bioremediation products, spill prevention and containment products, cleansers and degreasers.
- Sarva Bio Remed LLC. – the environment biotechnology company that manufactures bioremediation products to remediate oil pollution at source and offers products off the shelf.
- BioTreatment Inc. – soil and groundwater remediation contractor, specializing in cleaning up contaminated soil and groundwater, using bioremediation as the lead technology.

Identified Bottlenecks[49]
The current limiting aspects of bioremediation technologies are:
- Bioremediation is limited to those compounds that are biodegradable. Not all the compounds are susceptible to rapid and complete degradation.

47 EY internal experts; http://www.eosremediation.com/
48 http://www.environmental-expert.com/companies.aspx?word=bioremediation%20technologies&idkeyword=5234; Company websites
49 *Bioremediation. An Overview*, M Vidali, 2001, IUPAC Pure Appl. Chem.,Vol 73, No 7 pages 1163-1172, 2001; *US Bioremediation Market*, Frost & Sullivan, 2003; EY internal experts

- Biological processes are often highly specific. Important site factors required for the success include the presence of metabolically capable microbial populations, suitable environmental growth conditions and appropriate levels of the nutrients and contaminants.
- It is difficult to extrapolate from bench and pilot-scale studies to full-scale field operations.
- Research is needed to develop and engineer the bioremediation technologies that are appropriate for the sites with complex mixtures (solids, liquids, and gases) of contaminants that are not evenly dispersed in the environment.
- Bioremediation often takes longer than other treatment options (excavation, removal of soil or incineration).
- Regulatory uncertainty remains regarding acceptable performance criteria for bioremediation. There is no accepted definition of "clean" and evaluating performance of bioremediation is difficult. There are no acceptable endpoints for bioremediation treatments.
- Many Environmental consulting and engineering firms are apprehensive about using new technologies, in fear of being sued by the site owners.
- Apprehension with introduction of foreign agents – GEMS; Concern with transfer of antibiotic resistance to and from other bacteria bioremediation agents.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for the Future Implementation [50]
There are no companies in Estonia, that we are aware of, who currently have bioremediation products or services on the market.

However, two different types of potential market players have been identified that represent a first base that could be taken into account to develop this business field: environment service companies and industrial groups with projects to limit their environmental footprint.

Environment service companies: these companies are focused mainly on waste management programs, environmental licenses applications, soil and groundwater monitoring. They have the experience in leading remediation projects; however no use of the bioremediation techniques has been identified.

Endogenous:
- AS ÖkoSil: founded in 1997, responsible for the 10-year-long remediation work of the radioactive tailings pond in Sillamäe (completed in October 2008). The company specializes in environmental technology and waste management.
- OÜ IPT Projektijuhtimine: founded in 2000. The main activities include geotechnical field investigations, geotechnical engineering, supervision of earthworks and environmental site assessment (including: soil sampling and analysis, groundwater sampling and analysis, soil and groundwater monitoring, recommendations for remediation)
- OÜ E-Konsult: Activities include: environmental impact assessment, expertises and investigations, applying for environmental licenses and feasibility studies)

Exogenous:
- Ragn-Sells AB (Swedish): Resource and waste management. Founded in 1966 with an office in Estonia.

Industrial groups with projects to limit their environmental footprint (to comply with the strict regulations, limit high environmental taxes and develop better brand image): these groups have engaged research and development projects, including the remediation projects, which demonstrate their willingness to engage in such processes. However, no projects including bioremediation have been identified.

Endogenous:
Viru Keemia Grupp AS (the largest oil shale processing company in Estonia):
- Polluting processes have been terminated, such as generator gas cleaning with arsenic, scattering of oil coke with water and oil pitch storage. In the future VKG plans to complete an environmentally safe storage area for oil coke and clean up the old oil coke hills.
- Research and development projects are also targeted on the improvement of oil shale industry's technological processes (ATP technology plant (technology invented in Canada) to increase oil yield for shale and improve the environmental impact of the produced solid residue, development of thermal processing that causes destruction of the shale and results in formation of various valuable chemical substances, mainly phenolic compounds, Fluid Catalytic Cracking (FCC) for splitting large molecules in the boiling range into smaller, more valuable molecules).

50 Ernst & Young interviews and market analysis; Company websites; www.biotech.ee

Silmet AS (rare metal producer)
- All waste discharges to tailings pond have been stopped through the reuse of the different wastes (ex: utilization of nitric solutions (NaNO3+NH4NO3) to produce liquid fertilizers)
- AS Silmet Grupp with the Estonian government established a separate company, AS ÖkoSil, for the remediation of the Sillamäe tailings pond. AS Silmet also acted as a cooperation partner of the project.

Exogenous:
Estonian Cell AS (aspen pulp mill, owned by Heinzel Group from Austria, Larvik Cell from Norway and European Bank for Reconstruction and Development)
- The implemented thermo-mechanical process is more environment friendly than the traditional process and a large biological water treatment plant has been set up to treat effluents
- Research programs are being conducted to reuse waste (bark, sludge from the biological water treatment plant) as energy source or agricultural compost.

Supporting Research and Development for the Field[51]
Research and development is ongoing in several institutions on bioremediation and waste treatment. Furthermore, it is important to note that the competences in the environmental monitoring and management, in soil science, in the wastewater management, in microbiology, metagenomics and bioinformatics, support the development of this field.

Existing departments at universities related to R&D:
- University of Tartu (Institute of Molecular and Cell Biology (Gene Technology), Institute of Technology (Environmental Technology), Institute of Ecology and Earth Sciences (Geography)
- Estonian University of Life Sciences (Institute of Agricultural and Environmental Sciences (Environmental protection), Institute of Forestry and rural Engineering (Water management)) – Estonian University of Life Sciences offers specific education on water management (Engineering Department, doctorate program) and on grassland, soil and field crop science (Agricultural Sciences Department, doctorate program).
- Tallinn University of Technology (Faculty of Chemical and Materials Technology (Environmental and Chemical Technology) Faculty of Civil Engineering (Water Engineering)) – focus on wastewater treatment technologies.

There are relatively numerous research projects in Estonia on bioremediation, and even more on supporting subjects. Some examples are:
- In 1999, a small pilot willow plantation was established at Aarike to study the possibilities of the usage of willows for biomass production and wastewater purification (phytoremediation of nutrient enriched waste water).
- Master of Arts thesis "The use of bioremediation for the enhancement of biodegradation in the semi-coke." 2006
- Research project: Processes at interfaces and in condensed phases and their application in environmental technologies – basic research that will be applied in the development of effective environmental technologies including in the remediation of contaminated soils.
- Research project: Genetic impact of bio- and phytoremediation on formation of microbial populations in oil- and phenol-polluted semi-coke fields
- Research project: Molecular structure of the plasmids of five Pseudomonas strains before and after bioaugmentation of microcosms and field semi-coke test plots – This project followed the isolation of these five strains effective on phenol biodepollution (applicable for oil shale mining pits). This project is stopped and has not led to any applied research though a potential bioaugmentation product could be envisaged.
- Research project: Investigation of the development of microbial consortia in a newly established horizontal flow soil filter and the enhancement of nitrogen removal through bioaugmentation by adding microbial consortia from a similar environment
- Research project: Metagenomic and genomic approaches in studying of microbial biodegradation: A case study – the Baltic Sea water
- Research project: Catabolic performance of microbial communities in oil-contaminated Baltic Sea water and biodegradative plasmid genome organisation and evolution in bacteria of this ecosystem
- Research project: Investigation of hydro-physical parameters of sludges for optimisation of biodegradation of petroleum hydrocarbons in biopiles.

51 Ernst & Young interviews; ETIS database; Institution websites; Pubmed; European & US patent agency

No patent application has been identified for the bioremediation, wastewater, biodegradability, biosludge, biotreatment, phytoremediation or biodepollution

Public funding for environmental projects exists from the Estonian government (for example: Enterprise Estonia provides funding for VKG research and development projects) and from EU (especially in link with oil shale pollution).

Summary

Strengths ■ Existing research on bioremediation in several institutes that have led to potential for the product development (e.g. microbial strains for phenol de-pollution). ■ Existing competences in microbiology (including metagenomics, bioinformatics), environmental technologies (including waste management), environment monitoring, soil and hydrologic sciences representing a support to this field. ■ Existing Estonian companies with experience in environmental project management, including very large projects (Sillamäe tailings pond remediation). ■ Important government and EU support combined to very deterring taxes pushing industrial companies to invest in environmental projects.	**Weaknesses** ■ No identified companies involved specifically in bioremediation. ■ No products or services on the market illustrating the lack of transfer of results from basic research into applied research ■ Lack of patent application.
Opportunities ■ Important developing market. ■ Bioremediation products exist as market products abroad ■ Positive public perception for this "natural" waste treatment process. ■ Important potential of gene technology application to bioaugmentation through the production of optimized genetically engineered micro-organisms (supported by the results obtained through metagenomics). ■ Increasing international concern on pollution and opening of new markets through emerging countries.	**Threats** ■ Market highly dependant on regulations and regulatory standards. ■ Remaining uncertainties regarding the acceptable performance criteria for bioremediation (there is no accepted definition of "clean"). ■ Difficulty to extrapolate from bench and pilot-scale studies to full-scale field operations, coupled with the frequent necessity to work on a per project basis (due to complex dispersion of pollutants and hydrogeological properties of the site). ■ Apprehension with the introduction of genetically engineered micro-organisms in the soil, limiting the potential of gene technology in bioremediation.

Conclusion about the Potential for Estonia

From the international point of view, bioremediation is an existing but still largely innovative and quickly developing industry field.

For Estonia, it could be considered as a short- to mid-term field in which the country has already taken some first steps. The experience in environment remediation projects coupled with the existence of dedicated research are elements to build on. Important incentives from the Estonian government and EU have also initiated interest in new remediation solutions from industrial groups.

1.5 Industry 5: Energy Industry

1.5.1 Bioenergy

Introduction

Definition of the Field
Bioenergy comes from any fuel that is derived from biomass – recently, living organisms or their metabolic byproducts. Unlike other natural resources, such as petroleum, coal and nuclear fuels, bioenergy is a renewable energy source. Like all methods used to generate energy, the combustion of biomass generates pollution as a by-product. However, because the carbon in biofuels was recently extracted from atmospheric carbon dioxide by growing plants, the combustion of a biofuel does not result in a net increase of carbon dioxide in the Earth's atmosphere.

Biomass can include feedstock, wood and wood wastes from forestry industry; agricultural residues from harvesting or processing; energy crops grown specifically for energy applications; food waste from the food and drink manufacturing, preparation and processing; post-consumer waste; industrial waste and co-products from manufacturing and industrial processes; municipal green wastes; sewage sludge etc.

This field is expected to lead to an even larger contribution to global primary energy supply, significant reductions in greenhouse gas emissions, improvements in energy security and trade balances by substituting imported fossil fuels with domestic biomass, opportunities for economic and social development in the rural communities, scope for using wastes and residues, reducing waste disposal problems, making better use of resources and potentially other environmental benefits.

Examples of International Products and Services
Among the recent initiatives in this field, a couple of international solutions (European and American) have been developed:

- Genetic engineering to produce yeasts that can create highly efficient biofuels (Amyris Biotechnologies Inc., USA)
- Biogas pre-treatment and production, including a unique fermentation process that maximizes ethanol output to obtain bioethanol as a fuel for about half the current price (after taxes) of petrol in the US (BioGasol, Denmark)
- Proprietary gasification technology that converts black liquor (a waste stream in pulp and paper mills) into high-quality synthesis gas which can then be processed into a variety of advanced biofuels or green chemicals or used to drive turbines to make electricity (Chemrec AB, Sweden)
- Low-cost methods for developing ethanol by using a wide variety of input materials, such as biomass, agricultural and municipal wastes (including wood chips and old tyres) and using proprietary micro-organisms and patented bioreactor designs to produce feedstock-flexible ethanol (Coskata, USA)
- An engineered group of new enzymes used in a one-step fermentation process to produce biofuels that have higher energetic content than ethanol or butanol and have fuel properties essentially indistinguishable from those of gasoline, diesel and jet fuel starting from low-carbon, natural sources of sugar, such as sugar cane and cellulosic biomass (LS9, USA)
- New generation of microbes, yeasts and bacteria for rapid break down of the components of biomass in order to convert a range of sugars and polymers to ethanol (Mascoma, USA)

International business potential

International Market Size and Growth[52]

- Biomass is one of the fastest growing electricity sources in Europe. Its share in EU-27 primary energy production has reached 10% in 2006 showing a steady growth of 5-9%. At the same time, other energy sources, such as coal, oil, and gas saw their shares decreasing over the period of 2001-2006.
- Based on a mature technology, biomass sector is well positioned to continue expanding its share in primary energy and electricity production. Its main advantage over other renewable energy sources is a stable power supply that is suitable for base-load service. Life-cycle net carbon emissions per unit of "bioelectricity" are below 10% of the emissions from fossil fuel-based electricity. This leads many to accept biomass as "carbon-neutral" energy source.

52 *Biomass – a Solid Outlook for the Growing Market*, Frost & Sullivan; BIOENERGY – A SUSTAINABLE AND RELIABLE ENERGY SOURCE; A review of status and prospects; IEA Bioenergy, 2009; Datamonitor: Demand and Supply-side Dynamics in the EU Biofuels Market (BFEN0357); Demand and Supply-side Dynamics in the EU; *Biofuels Market*. Datamonitor, 2008

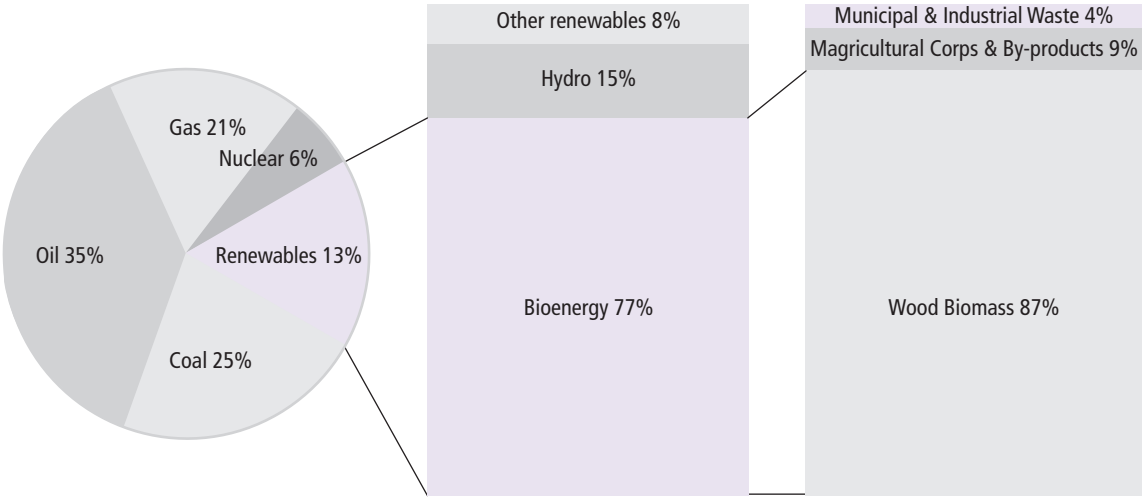


Figure 8: Share of bioenergy in the world primary energy mix

- While other sources of biomass are gaining in popularity, wood and wood wastes are a prime biomass source at present, accounting for about 70% of overall biomass utilized in the EU. Since transportation can add significantly to the feedstock costs and a total process carbon footprint, the biomass industry has initially flourished in the countries with large domestic wood and paper industries like Finland and Sweden. However, as urban and industrial waste disposal is increasing in scale and expenses, many waste management companies and investors are looking for the ways to turn landfills into waste-to energy plants which produce electricity or heat. At the same time, technology developers are developing new and more efficient ways to utilize the waste and convert it into something valuable, such as biogas resulting from degrading biological material providing a source of renewable energy from organic waste materials for a small labour input.
- Today, biomass generates energy representing around 10% of annual global primary energy consumption. This is mostly traditional biomass used for cooking and heating.
- There is significant potential to expand biomass use by tapping the large volumes of unused residues and wastes. The use of conventional crops for energy use may also be expanded with careful consideration of land availability and food demand.
- In the medium term, lignocellulosic crops (both herbaceous and woody) could be produced on marginal, degraded and surplus agricultural lands and provide the bulk of the biomass resource. In the longer term, aquatic biomass (algae) could also make a significant contribution.
- Bio-ethanol is by far most important biofuel product, representing more than 85% of the total biofuel production. The bioethanol production is composed mainly by sugarcane and corn, and biodiesel uses in a major part soybean.
- At the international level, the United States is driving this subject. On December 19, 2007, US President signed into law the energy independence and security act (EISA), which constitutes an important pace of USA in the biofuel economic strategy. It consists mainly of expanding biofuels' share of the transportation fuel market from 4% to 20% by 2022; increasing the volume of renewable fuel to be blended into nation's fuel supply to 36 billion gallons by 2022, and a major fraction of it must come from cellulosic or other advanced biofuels; increase of authorized funding for the existing biomass research and development program by 50% and extend it through 2010.
- In Brazil, more than 45% of all energy consumed comes from renewable sources, which makes Brazil's energy mix one of the cleanest in the world. Brazil is currently investing more than US$15 billion in new ethanol mills.
- China is the world's third largest producer after United States and Brazil. Renewable energy consumption represents 7.5% of its total energy consumption and the country expects an increase to 15% within 2020.
- In Europe, France, Germany and Spain are all major producers of bioethanol, whereas France and Germany are the largest producing countries. In 2007, 578 and 394 million litres of bioethanol were produced in these markets, respectively. One company in France (Tereos) accounts for 56% of total bioethanol production. Verbio has the largest amount of capacity in Germany with 41% of capacity and accounts for 6.3% of the country's total capacity.
- Italy and Austria produced 413 and 303 million litres of biodiesel in 2007, respectively.
- The UK produces the least amount of bioethanol of the large Western European markets, having produced 20 million litres in 2007. Nevertheless, a number of companies, including Ensus, Ineos and Abengoa, have announced plans to increase capacity in the UK.

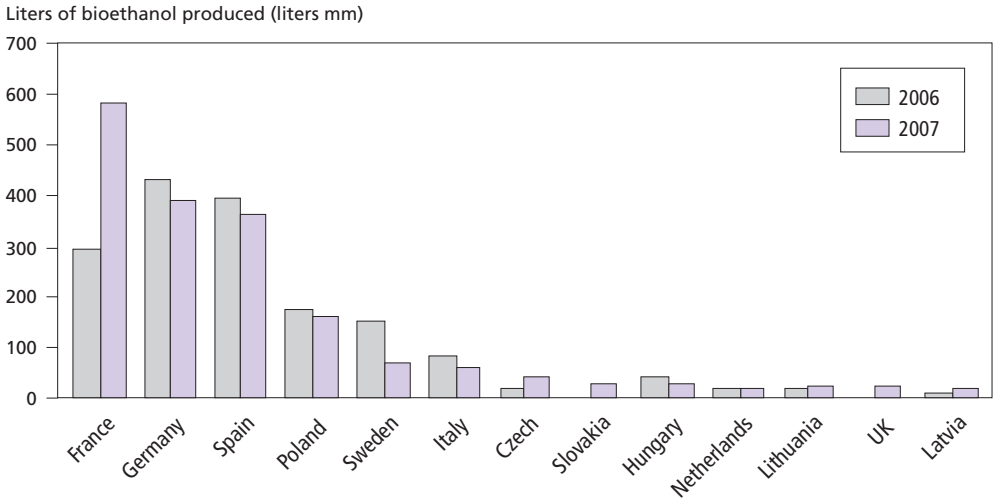


Figure 9: France, Germany and Spain are all major producers of bioethanol

- Governmental support and strong initial take-up of biofuels are the principal reasons for the strong production base in Germany. Leading producers in these markets include some of the largest producers of biodiesel in the world. The largest of these is the US company Archer Daniels Midland, whose plants in Hamburg, Leer and Mainz represent 16% of total production capacity.
- EU Biomass Action Plan released in December 2005, together with the Directive on the promotion of the electricity from renewable energy sources, outlines a pan-European framework for the biomass sector development. While a set of specific market stimulating mechanisms vary from country to country, Finland as the most mature and largest market in Europe, provides a great example for the developing markets to study from and follow.
- The Finnish National Climate and Energy Strategy among other renewable energy sources specifically stress and promote the use of forest chips, agrobiomass fuels, biogas and the small-scale use of wood, which is supposed to take place through the increased consumption of wood pellets.

Trends and Developments

- Bioenergy is already making a substantial contribution to meeting the global energy demand. And it will be expanded very significantly in the future, providing environmental benefits as well as contributing to energy security, improving trade balances, providing opportunities for social and economic development in rural communities and improving the management of resources and wastes.
- Bioenergy could sustainably contribute between a quarter and a third of the global primary energy supply in 2050. It is the only renewable source that can replace fossil fuels in all energy markets – in the production of heat, electricity, and fuels for transport.
- Many bioenergy routes can be used to convert a range of raw biomass feedstocks into a final energy product. Technologies for producing heat and power from biomass are already well-developed and fully commercialized.
- This segment constitutes a high priority for many developed countries with regard to their dependence from importation of oil and the rising of prices of that raw material, consequence to the augmentation of demand, especially for feeding the growth of China.
- Fuel retailers may seek to invest in the refining capacity for second-generation biofuels, produced from anything biological, including wood chippings, leaves and grass, providing a much cheaper way of producing fuel than the current methods.
- Of all of the major fuel retailers, Shell has been the most active in this regard to date. In 2002 they purchased a share in Canada-based Iogen Corporation to accelerate development and deployment of cellulosic ethanol. In addition to its share in Iogen, Shell has also entered into collaborations with other rather small companies like Choren (production of biomass to liquid technology), Codexis (enzyme conversion), Virent (development of biogasoline) and a joint venture called Cellana covering the development of marine algae for vegetable oil.
- Preem Petroleum in Sweden is another example of a company that has invested in second-generation technology. In June 2008, it took a 60% stake in SunPine AB (biorefinary that has recently opened a new plant in Pitea and converts crude bio-oil by-products of pine pulping into second generation biodiesel), along with Sveaskog Forvaltnings AB, a supplier of sawlogs, pulpwood, and bio-fuel, and Sodra Group AB, a provider of forestry services and a producer of wind power. The deal was reportedly worth a total of €16 million. SunPine is a bio-refinery that has recently opened a new plant in Pitea, Sweden, and converts crude bio-oil by-products of pine pulping into second-generation biodiesel.

Time to Market
Long research and development period and significant investment is required within this business field.

Important International Market Participants
This bioenergy industry sector is submitted to a huge and complex competition dominated by the USA and relying on strategic patent position of the different launched or under development technologies.

Main actors in the Biomass industry include:
- Cellulosic ethanol from wood chips and forest residue: Range Fuels (USA), Dynamotive Energy Systems (Canada)
- Developing enzyme that can be engineered into cellulose-rich plants to make them easier to convert to fuel: Cilion (USA), Mascoma (USA), Edenspace Systems (USA), CR-6 Tehcnologies (USA), Agrivida (USA)
- Biomass-tohydrocarbons conversion processes for liquid fuels: Virent Energy Systems (USA)
- Methane stored in garbage and minimal waste converted to power which is then injected into electric grid: Zegen (USA)
- Biodiesel from Algae: Greenfuel Technologies (USA), Solazyme (USA)
- Synthetic biology engineering microbes to produce commercially feasible biofuels: Amirys technologies (USA), Codon Devices (USA, LS9 (USA), Gevo (USA), Biobutanol, Cobalt Biofuels (USA)

Identified Bottlenecks
- Current methods of producing bioenergy are not sufficient to meet renewable energy demand. For example, the production of ethanol from corn meets at most 15 or 20% of US energy need.
- European biofuels producers have been damaged by the subsidies provided to US producers.
  In 2004, the US adopted a law whereby the production of biodiesel can be subsidized by approximately €200 per ton. All that producers need to do in order to claim the subsidy is add a small amount of mineral diesel to biodiesel. The product can then be exported to Europe, where local subsidies can also be claimed on it. The European Biodiesel Board has argued that in some cases this has caused US biodiesel to be sold in Europe below the market price. As a result of subsidies to US biofuel producers, imports of biodiesel from the US have increased from approximately eight million litres in 2005 to approximately 1.1 billion litres in 2007. As such, US imports of biodiesel account for approximately 20% of all biodiesel used in the European Union today. Some European biofuels producers have reacted by engaging in a practice known as 'splash and dash', which enables them to claim US subsidies. The practice is undertaken by European producers shipping biofuels to the US, where a small amount of petroleum is added. This enables them to claim the full US subsidy. Unsurprisingly, this has provoked a considerable amount of concern amongst politicians and environmental groups which have claimed that it makes a mockery of biofuels' environmental credentials.
- Nevertheless, there are signs that European biofuel producers may be affected less by US imports in the future. In June 2008 the European Commission launched an investigation into subsidized US biodiesel, drawing on anti-dumping and anti-subsidy legislation. The goal of the investigation is to find out whether imports of US biodiesel break international trade rules because of subsidies. Although a conclusion has yet to be reached, a likely outcome is that a tariff will be placed on US imports, offering domestic producers some reprieve.
- As a result of US imports, European producers of biofuels have spare capacity which has a negative impact on biofuel producers' finances.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation

Existing products and services:
- Wood-derived products, equipment and services (maintenance) for combustion and heating systems

Largest endogenous companies involved in the bioenergy field
There are 2–3 companies really involved in the biotech process (NordBioChem, Muuga Sojatehas and Werol).
- NordBioChem LLC
  Privately-held company that owns a strong technological platform for manufacturing chemicals and materials that come from renewable source and are priced competitively to petro-based alternatives. The technological platform starts with lactate fermentation, followed by chemical derivatizations.
  The main focus of the company is on acrylates, propylene glycol and PLA.

- AS Muuga Sojatehas
  It engages in the process and production of soybean meal and soybean oil for poultry feed concentrate and biodiesel. As of May 8, 2006, Muuga Sojatehas AS is a subsidiary of Russkije Masla.
- Werol Tehased Ltd (refined rapeseed oil, rape cake, rapeseed expeller, feed oil)
  Offers long-term solutions for the cultivators, producers and consumers of the neighbourhood concerning grain-producing rapeseed, high-quality food oil and energy-rich fodder.
- Graanul Invest
  Founded in 2003, AS Graanul Invest is the largest producer of pellets in the Baltics.
- OÜ Cellufuel
  Company that produces wood and straw pellets from Estonian raw materials. The company's administrative and research and development departments are located in the capital, Tallinn.
  Cellufuel has a modern factory with innovative and nature friendly production methods that intends to stay on the leading edge and introduce new renewable material based products in cooperation with the company's research department. The factory is one of the largest in Estonia, therefore, the production capacities are sufficient to fill large orders using inexpensive marine transportation. The production has recognized European certificates (SGS) for the highest quality pellets for home users as well as cost efficient industrial grade pellets.
- Tamult AS
  Privately owned company that specializes in two main activities: heat engineering (solutions for biomass/fuel fired combustion systems – designn, manufacturing, assembly and services) and bulk materials handling equipments design, manufacturing and erection.
- Baltic Biogas OÜ
  Deals with the development of the biogas station in Tallinn, operating on the basis of biodegradable raw materials from food processing and agricultural holdings in and near the city. The founders of OÜ Biogaas were, in addition to Baltic Biogas OÜ, also agricultural holding Malanell and Indrek Tiidemann, chairman of the board of AS Terts, who has extensive experience in thermal and electrical generation from biogas on the basis of the landfill gas in Pääsküla. Biogas is a gas fuel obtained via anaerobic fermentation, which is comprised of 50-70% methane (CH4), 30-40% carbon dioxide (CO2) and other components, such as N2, O2, NH4, H2S. It is possible to obtain biogas through the course of natural processes from marshes, bogs and landfills and special fermenters using manure, wastewater, woody biomass and other biodegradable waste.
- Biodiesel plant: Kadarbiku Plant (bioethanol and biodiesel in Tallinn)
- OÜ Mikrotaim
  The company has a plant tissue culture laboratory capable of developing protocols for practical micropropagation, initiating aseptic plant tissue cultures and producing micropropagated plants. They are also investigating the influence of various factors affecting initiation of cultures and successful biomass production in vitro.
- Väo Power Plant (fuelled by woodchips)

Largest exogenous companies involved in the bioenergy field:

- Terts AS
  Develops biogas collecting systems and systems monitoring
- MGT Power
  The British company MGT Power wants to buy from the Baltic countries a million tons of woodchips a year starting from 2012 for the needs of a woodchip-fuelled power plant. The capacity of the power plant they are planning to build is 295 megawatts and it will be built at a cost of 500 million pounds.

Supporting Research and Development for the Field

A couple of institutions and universities are involved in this topic:

- Tallinn University of Technology, Faculty of Mechanical Engineering, Department of Thermal Engineering
- Estonian University of Life Sciences, Institute of Agricultural and Environmental Sciences
- Tallinn University of Technology, Faculty of Chemical and Materials Technology
- University of Tartu, Institute of Molecular and Cell Biology

The Centre of Renewable Energy from the Estonian University of Life Sciences is deeply involved with this subject:

- The Centre of Renewable Energy of the Estonian University of Life Sciences – the main goals are to start, coordinate and develop interdisciplinary scientific and developmental co-operation in the field of renewable energy. In 2006-2008, the centre has concentrated primarily on bio energy and in particular on bioenergy from grasses and agricultural crops, biogas, short rotation forests, biomass from the forestry, technological solutions for production and use of renewable energies, economical and social aspects of production and use of biofuels.

There are a significant number of research and development projects that are on-going, related to the biomass and bioenergy subjects in Estonia:

- BioH2 – Renewable production of H2 using biological systems
- Efficiency of biogas production from Estonian biomass, by-products and waste, and kinetics of anaerobic fermentation
- Fundamentals of thermochemical co-processing of fossil and renewable fuels and organic wastes
- Optimization of the conversion processes of high molecular organic matter: products chemical composition, qualities and upgrading
- Renewable Energy Resources of Estonia and Enlargement their use in Energy
- Efficiency of biogas production from Estonian biomass, by-products and waste, and kinetics of anaerobic fermentation
- High efficiency consolidated bioprocess technology for lignocellulose ethanol (HYPE)

One identified patent application with NordBioChem on the process of conversion of waste polymeric materials into hydrocarbon fractions. The present invention relates to a method of conversion of waste polymeric materials into hydrocarbon fractions, gasoline and diesel oil. According to the present invention the conversion of waste polymeric materials can be carried out at the presence of the catalyst which includes one or more of the elements of transition metals, where in, at least, one of the elements of the same metals has a various degree of oxidation.

Business financing support:
Existence of specialized VC's

- Baltics Small Equity Fund (BSEF) a generalist venture capital firm that invests in small and medium size enterprises in Estonia, Latvia, and Lithuania,
- BaltCap Private Equity Fund (BaltCap OÜ): a generalist private equity and venture capital investor in the Baltics

Summary

Strengths	**Weaknesses**
■ An important biomass feedstock available in Estonia to valorise. ■ A couple (2-3) of companies having already a strong interest in biotechnology use of the biomass to produce renewable energy (NordBioChem, Muuga Sojatehas and Werol Tehased). ■ A new patent application (priority date in 2007) on a process of conversion waste polymeric materials into hydrocarbon fractions, gasoline and diesel oil. ■ A critical mass of companies in solid biofuel energy industry both endogenous and exogenous (combustion systems mainly) but limited biotech competences. ■ A small research and development workforce in academia working mainly in the wood-derived associated subjects. ■ A couple (3-4) of Key Opinion leaders (KOL). ■ A critical mass of project submitted for grants and funding.	■ An insufficient critical mass of industry with strong research and development competences. ■ Only one patent application identified in Estonia leading to a very limited industrial property status. ■ Lack of government funding compared to other countries. ■ Lack of research and development biotech competences in this field. ■ Lack of dedicated Master of Science and PhD specific programs. ■ Lack of Venture Capitalist Companies. ■ Lack of specialized Tactical Technology Offices for valorisation purposes.
Opportunities	**Threats**
■ A growing market and a growing demand for the type of renewable energy. ■ An interest for the internal market. ■ A couple of opportunities to in-license for the internal and regional market.	■ A huge international competition and in particular a high pressure from the USA. ■ A need for major public investment to remain in such a competition. ■ Existing European countries very advanced in this subject.

Conclusion about the Potential for Estonia

Bioenergy and biomass industries represent huge and growing markets in the world. However the competition in these fields is of a high complexity leading to very limited opportunity for a new entrant, such as Estonia except for national or regional applications using existing or under development technologies developed by third parties and in-licensed by Estonian company or government.

Clean technologies under development that could decrease dependence to petroleum through in-licensing of these technologies for geographical territory, such as the Baltic States and Scandinavian, for instance:

- Cellulosic ethanol from wood chips and forest residue (Range Fuels or Dynamotive Energy Systems) – interesting for Estonia because of its amount of wood chips and forest residue available
- Developing enzymes that can be engineered into cellulose-rich plants to make them easier to convert into fuel (Cilion, Mascoma, Edenspace Systems, C5-6 Technologies, Agrivida)
- Biomass-to-hydrocarbons conversions processes for liquid fuels (Virent Energy Systems)
- Methane stored in garbage and animal waste converted to power which is then injected into the electric grid (Zegen)
- Biodiesel from algae (GreenFuel Technologies, Solazyme)
- Synthetic biology, engineering microbes to produce commercially feasible biofuels (Amyris technologies, Codon Devices, LS9, Gevo)

1.6 Industry 6: Healthcare

1.6.1 Therapeutic Products

Introduction

Definition of the Field

The Therapeutic business field covers the discovery and development of new entities for novel therapeutic approaches. Entities (or active substances) can be either small chemical molecules, biologics (therapeutic proteins, monoclonal antibodies, gene or cell therapy products, peptides) or a medical device containing an active substance.

Therapeutic development is highly dependent on therapeutic areas of interest. Therapeutic areas include broad fields, such as oncology, central nervous system (CNS), cardiovascular (CV), inflammation and autoimmune disorders but also smaller special areas, such as reproductive medicine.

In addition to the aspects of therapeutic areas, drug development is also extremely dependant on the structure of clinical trials and translational and clinical research. Translational medicine or translational research is an emerging field that aims to integrate basic scientific research during the discovery phase of drug development with clinical research, and vice versa, to expedite marketed therapies for patients. The bi-directional nature of this field is what differentiates translational medicine from traditional pharmaceutical research. Namely, translational research represents a single, continuous, two-way spectrum – often termed "bench to bedside". In this spectrum, scientific insight emerging from preclinical experiments continuously feeds into the design of a clinical study (bench to bedside) and information from clinical trials is used to refine preclinical experiments and improve understanding of human disease during the early phases of drug discovery (bedside to bench). This approach to drug discovery and development has resulted in the identification of biomarkers – measurable molecules in the human body that can be correlated with a disease or can provide a measure of the impact of a drug (e.g. toxic or adverse effects).

Examples of Products and Services

Therapeutic products are mainly split into families of the following molecules:

Small molecules: 

Vaccines: 

Antibodies: 

Hormones and therapeutic proteins: 

Gene or cell therapies:  

Oncology therapies:
In 2007, the sale of cancer targeted therapies accounted for over 50% of global oncology sales growing by around 17% in a year. These include the monoclonal antibodies (MAbs) and represent one of the highest selling classes of biologics. Growth was fuelled by greater market penetration of these innovative targeted therapies, both in terms of earlier usage in the treatment process and in combination therapies.

Current leading cancer brands include Rituxan, Herceptin and Avastin from Roche/Genentech, Arimidex from Astra-Zeneca, Gemzar from Eli Lilly, Gleevec and Zometa from NovartisCamptosar and Sutent from Pfizer.

CNS therapies:
In 2007, the sale of antidepressants accounted for nearly a quarter of sales, growing around 2% annually versus anti-Alzheimer sales which accounted for around 3% of sales but is one of the fastest growing segments with an annual growth rate of 16%. Sales of CNS products were fuelled by new product formulations and combinations, the launch of novel, new classes of drugs and gene therapies, a greater penetrations of attention deficit hyperactivity disorder (ADHD) products within the adult market, which helped to offset the impact of generics and decline in the prescription of antidepressants within the pediatric population.

Leading CNS brands include Zyprexa & Cymbalta (Eli Lilly), Seroquel (AstraZeneca), Effexor (Wyeth), Lexapro/Cipralex & Ebixa/Namenda (Forest/Lundbeck), Topomax, Concerta, Duragesic & Remicade (J&J), Lyrica & Geodon/Zeldox (Pfizer), Stilnox (sanofi-aventis), Ability (Bristol-Myers Squibb), Depakote (Abbott), Imigran, Paxil, Lamictal & Wellbutrin (GlaxoSmithKline), Adderall XR (Shire).

Cardiovascular therapies:
In 2007, the sale of anti-dyslipidaemics and anti-hypertensives represented the major areas of sales of cardiovascular drugs. Leading drugs in both of these areas have lost patent protection in the last two years and will continue to lose protection, such as the Lipitor from Pfizer. In 2006, leading statins Pravachol (Sankyo Pharma/Bristol-Myers Squibb) and Zocor (Merck & Co.) lost their US patent protection and spending on statins may have fallen by 27.7% in 2007 in USA. Generic competition for leading anti-hypertensives, Norvasc (Pfizer) and Coreg (Roche/GSK) was introduced in 2007. These facts are impacting the CV market and will moderate overall growth in the CV market over the next few years, despite growth in the utilization of these drugs.

Leading brands involve Lipitor, Caduet & Norvasc (Pfizer), Plavix, Aprovel/Avapro (BMS/sanofi-aventis), Lovenox (sanofi-aventis), Atacand (AstraZeneca/Takeda), Cozaar Vytorin (Merck & Co), (Merck & Co), Crestor (AstraZeneca), Zetia (Merck & Co, Schering-Plough), Micardis (Boehringer Ingelheim), Seloken (AstraZeneca), Tricor (Abbott), Coreg (GSK/Roche), Tritace (sanofi-aventis), Lotrel, Diovan & Lescol (Novartis), Niaspan (Abbott).

Inflammation and autoimmune disorders:
In 2006, 96.2% of AIID therapy area is related to the target tumour necrosis factor-alpha (TNF-). From US$4.1 billion in 2003, sales of these anti-TNF products have grown at an impressive 36.5% CAGR to reach US$10.6 billion in 2006. While the rate of growth is set to decelerate, sales of US$17.8 billion in 2012 are forecast for the group, giving 9.1% CAGR overall across 2006–12. The bulk of anti-TNF sales are attributed to J&J/Schering-Plough's Remicade (infliximab), Abbott's Humira (adalimumab), Amgen/Wyeth's Enbrel (etanercept). The three products are all biologics and while Remicade and Humira are monoclonal antibodies (mAbs), Enbrel is a fusion protein based on a mAb fragment. The TNF- target is implicated in wide ranging diseases, allowing extensive growth through indication expansion. The products are approved for overlapping indications that include rheumatoid arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis and ankylosing spondylitis.

Reproductive medicine:
The standard in vitro fertilization (IVF) treatment regimen consists of a long downregulation protocol using gonadotropin releasing hormone (GnRH) agonists. This is followed by ovarian stimulation with follitropins or menotropins and finally ovulation induction through human chorionic gonadotropins (hCG). However, it was found that over 40 drug class regimens are used by physicians suggesting that there is really not much clinical difference between regimens, drug classes and brands.

Across the US and the western EU markets, there is a marked trend towards prescribing recombinant hCG products over urinary hCG. In contrast, Japan has a strong preference for urinary products with over 80% of hCG and 60% of follicle stimulating hormones (FSH) being prescribed in the urinary form.

According to physicians, the most common therapy regimen for infertility consists of a combination of drugs. Research fails to show which class is most effective in terms of pregnancy rates and live births. Therefore, physicians are able to tailor regimens to their own preferences and to individual patient need, a feature that is particularly evident in Germany.

Infertility drugs available in major European markets include follitropin–beta "Puregon" and follitropin–alpha "Gonal F", two rFSH from Organon and Merck Serono, urofollitropin "Bravelle", a uFSH from Ferring, corifollitropinalph "Org–36286", a long-acting FSH from Organon, menotropin "Menopur", a u hMG from Ferring, buserelin "Suprefact", a GnRH agonists from sanofi-aventis, ganirelix "Orgalutran", a GnRH antagonist from Organon and rFSH and rLH "Pergoveris" from Merck Serono.

International Business Potential

International Market Size and Growth[53]

Oncology therapies:

In 2007, the global anticancer market was estimated to be worth just under US$40.0 billion (increase of 14% in a year) and accounted for around 6% of global pharmaceutical sales. This includes the sales of cytotoxics, innovative targeted therapies and anti-hormonals, and excludes supportive care (such as surgery related sales, brachytherapy, recombinant growth factors, anti-emetics and serotonin antagonists etc.).

CNS therapies:

In 2007, the global sales of drugs to treat central nervous system (CNS) disorders was estimated to be worth over US$100.0 billion (+7% / year) and accounted for around 17% of global pharmaceutical sales. This includes the sales of antidepressants (21% of all CNS sales), anti-psychotics (17%), anti-epileptics (12%), analgesics (18%), hypnotics (5%), anti-Parkinson agents (3%) and anti-Alzheimer agents (3%).

Cardiovascular (CV) therapies:

In 2007, the global cardiovascular disease market was estimated to be worth just under US$86 billion (+10% /year) and accounted for around 12% of global pharmaceutical sales. This includes the sales of drugs in four key areas: anti-hypertensives representing around 45% of all CV sales, anti-dyslipidaemics (39%), anti-thrombotics (10%) and anti-coagulants (6%).

Inflammation and autoimmune disorders:[54]

Overall across 2006–12, sales from the auto-immune and inflammatory disorders (AIID) therapy area are expected to act as the major drivers of market growth. AIID sales are forecast to increase by US$11.9 billion over the years 2006–2012.

Reproductive medicine:[55]

Infertility is defined as the inability to conceive after a year of frequent unprotected intercourse.

The etiology of infertility may be diverse. In 2008, Datamonitor published that 30% of infertility cases are attributable only to the male partner and 30% only to the female partner. In 20% of cases infertility will be caused by some problem in both partners and in up to 10% of cases infertility remains unexplained.

The major causes for female infertility are the ovulation disorders. These are often caused by hormonal imbalances, which can be first cured through ovulation induction therapies and then through in vitro fertilization (IVF).

Datamonitor, 2008, estimates that in the seven major markets there are about 11.6 million women between the ages of 25 and 45 who suffer from infertility.

Trends and Developments

Oncology therapies:

Pharmaceutical research and development expenditures reached around US$44.5 billion in 2007, resulting in more than 600 medicines in clinical development to treat cancer. Many of these drugs represent potential breakthrough cancer treatments, while others involve possible new uses for existing medicines. Major efforts are focused on solid tumours (breast, colon, lung and prostate), although several novel approaches to cancer treatment are being evaluated, such as gene therapy, therapeutic vaccines and immunotherapeutic agents.

53 *Cancer, CNS and cardiovascular biomarkers*, Espicom, 2008
54 *Analysis of the Pharmaceutical Market to 2012–Segmented by Drug Target Family*, Datamonitor, 2007
55 *Stakeholders Insight: Infertility*, Datamonitor, 2008

CNS therapies:
Pharmaceutical Research and Manufacturers of America (PhRMA) estimated that US$44.5 billion has been spent on pharmaceutical research and development in 2007, resulting in nearly 250 medicines in clinical development to treat CNS disorders. Many of these drugs represent the potential breakthroughs in hard-to-treat diseases, such as Alzheimer's and Parkinson's disease or represent new drug classes for formulations to expand treatment options. PhRMA research showed the greatest focus on dementias and depression although several novel approaches to eating disorders were being evaluated in the clinic.

Cardiovascular therapies:
As mentioned above around US$44.5 billion was spent on pharmaceutical research and development in 2007 resulting in almost 300 medicines in clinical development to treat cardiovascular diseases. New medicines in development include mainly products for heart failure (around 30) and stroke (around 19).

New approaches include:
- Combinations aimed at improving cholesterol levels alone or with other risk factors, such as hypertension.
- Approved fixed-dose combinations: Pfizer's Caduet (amlodipine + atorvastatin), Merck & Co.'s Tredaptive (niacin + laropiprant) and Bayer's Simcor (niacin + simvastatin);
- Renin-inhibitors for hypertension, such as the first of new class Novartis' Rasilez (aliskiren) approved by the FDA in May 2007;
- Gene therapy treatment for coronary artery disease including for example the Generx from Cardium Therapeutics, an intracoronary infusion of an adenovector encoding the angiogenic FGF4 gene;
- Treatments aimed at enhancing HDL levels, such as cholesteryl ester transfer protein (CETP) inhibitors including anacetrapib (Merck & Co) and R1658 and R7232 (Roche). Avant Immunotherapeutics is also targeting CETP with its CETi vaccine currently in clinical trials;
- Lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitors for the treatment of atherosclerosis with darapladib and rilapladib from GlaxoSmithKline;
- Oral direct thrombin inhibitors, such as Pradaxa (dabigatran; Boehringer Ingelheim), the second oral direct thrombin inhibitor to reach the market in the EU;
- Oral direct factor Xa inhibitors for the treatment of venous and arterial thrombosis, including rivaroxaban (Bayer/Johnson & Johnson) and apixaban (Pfizer/Bristol-Myers Squibb);
- Gap junction modulation for the prevention of arrhythmias with Wyeth.

Inflammation and autoimmune disorders:
AIID have been forecasted to increase by 6.7% CAGR over the period 2006–12.

Reproductive medicine:
While prevalence rates have remained stable over the past 3 decades, the demand for IVF treatment has risen. Furthermore, there is an opportunity to increase the size of the IVF market by including homosexual couples and single mothers.

There is still an ongoing debate about whether to use GnRH agonists or antagonists. In addition, the reduced length of each cycle due to the use of antagonists is thought to be a very important advantage in terms of safety and patient convenience. As new data released demonstrates the efficacy of the drug we may see a shift towards increased use of antagonists in the near future.

Almost two-thirds of cycles are still performed with fresh, as opposed to frozen embryos. There may be a change in this trend as the preservation techniques improve. The main advantage of this will be that patients will not having to undergo too many ovary stimulation cycles. However, country-specific regulation against cryopreservation may represent an important threat to this market.

New treatment guidelines are likely to promote the increase use of mild stimulation protocols over long ones and the transfer of one single embryo rather than two or more. This is thought to increase the safety of the procedure, however there are concerns that it would lead to lower pregnancy rates and therefore increase the number of cycles that would have to be performed before IVF is successful.

Time to Market[56]
The time to market for drug development is worth 12-15 years with few particularities depending on the incidence of certain pathology allowing reduction in clinical trial timelines (one pivotal clinical study for a new and orphan indication versus phase II and Phases III clinical trials for broad indications with large number of launched products.

56 Ernst & Young

The time to market for a therapeutic product will be more and more closely related with translational research and the ability to accelerate development and clinical trials through optimized synergies between one particular substance and the use of clinical trials biomarkers as surrogate end-points. Translational research will strongly impact the future of clinical trials and development[57]. Early clinical studies will become more and more important as a "first into man" transition.

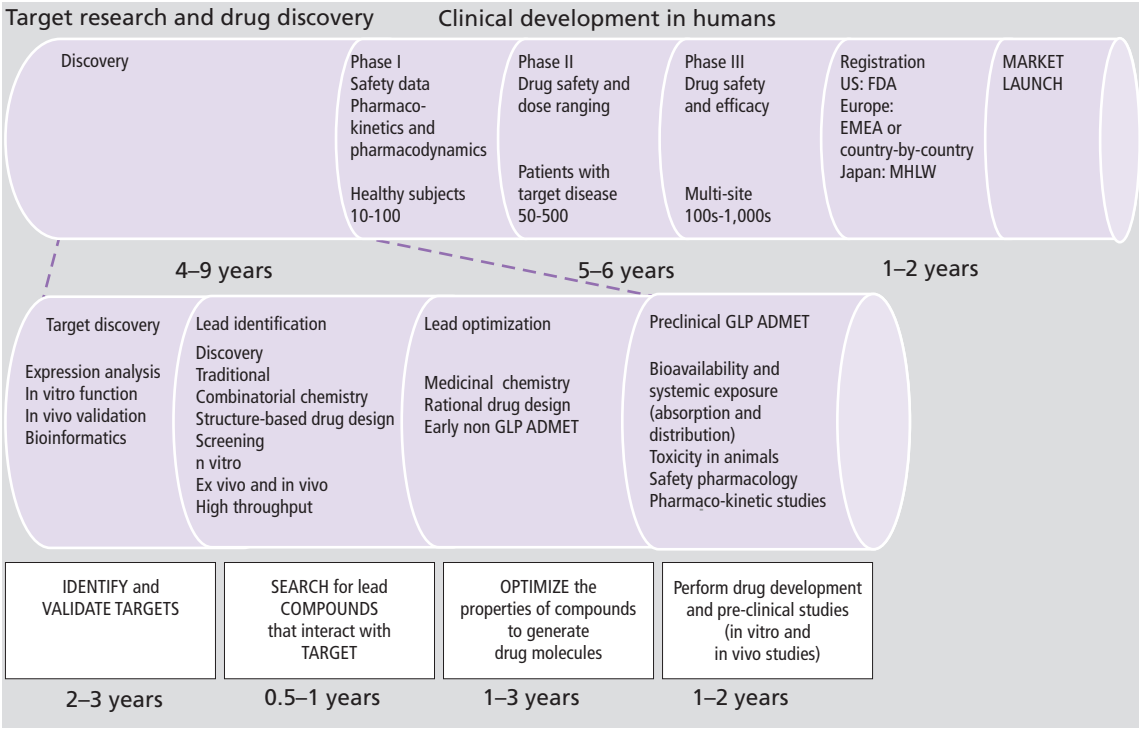


Figure 10: The time to market for drug development

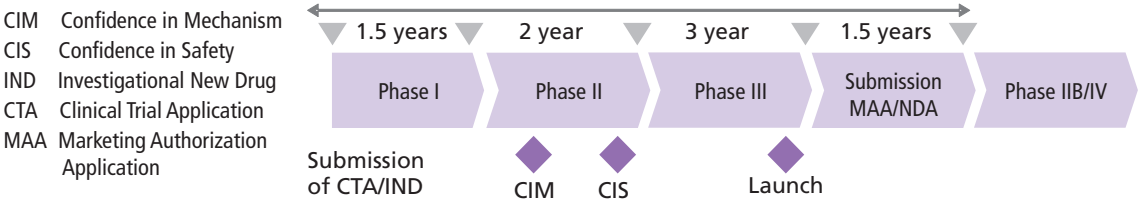


Figure 11: Current clinical development

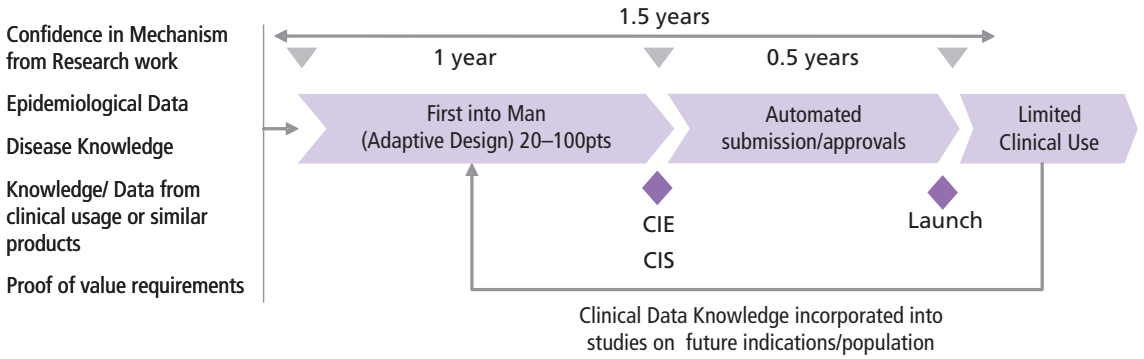


Figure 12: Clinical development in 2020

57 *Pharma 2020: Virtual R&D. Which path will you take?*, PWC

Important International Market Participants

Oncology therapies:

Cancer therapeutic is one of the largest therapeutic segments in terms of revenue, and it continues to attract investment from all the leading pharma-players. It is dominated by large pharma (such as AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck Serono, Novartis, Pfizer, Roche and sanofi-aventis) but has been joined by the biotechnology industry and drug-delivery specialists, including Amgen and Genentech (now part of Roche).

CNS therapies:

CNS therapeutics is one of the largest segments of prescription medicines in terms of revenue and has attracted significant investment from many of the leading pharmaceutical companies (AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Pfizer and sanofi-aventis). It also attracts interest from specialist pharmaceutical companies, such as Shire, which is a market leader in ADHD therapies, and Lundbeck, which is a CNS specialty outfit.

Cardiovascular therapies:

Cardiovascular therapeutics is one of the largest therapeutic segments in terms of revenue and continues to attract investment from all leading pharma players. It is dominated by large pharma – Pfizer, sanofi-aventis, Merck & Co, Bristol-Myers Squibb, AstraZeneca, Novartis, Takeda, Abbott, GlaxoSmithKline and Boehringer Ingelheim.

Inflammation and autoimmune disorders:

Inflammation and auto-immune disorders are a growing therapeutic segment with major big-pharma or bio-biotech players such as J&J, Schering-Plough's, Abbott, Amgen or Wyeth now Pfizer.

Reproductive medicine:

Reproductive medicine corresponds to a smaller therapeutic segment but it is still able to attract mid-size players, such as Organon and Feering or even big pharma players, such as Merck Serono and Sanofi-Aventis.

Identified Bottlenecks

Across all therapeutic areas, loss of patent protection and exclusivity is currently occurring for a broad number of molecules leading to a huge need for the pharmaceutical and biotech industry of novel innovative products. This need for new entities does represent a great opportunity for company or academic laboratories developing such innovative products.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation

The Estonian therapeutic development industry is mainly based on small companies with less than 50 employees. The Estonian therapeutic development industry market is mostly dominated by endogenous companies with more than 10 companies in the field as well as a couple of exogenous companies representing a real industry critical mass for Estonia. According to presentation EBio, 2007, Estonia has about 200 employees in the biotech companies.

The early stage of development of the health care biotech industry in Estonia as well as the lack of regular patent policy use is consistent with the privileged services business model. Services business model allow Estonian company to develop and launch relatively quick time to market products and services with short-term economic return but this model is also associated with limited economic return as well as low company value.
However, therapeutic product development requests product oriented business models with solid patent portfolio, high value creation, major long-term investments and high licensing revenues generated once the proof of concept in human has been achieved.

This discrepancy between the current Estonian health biotech industry characteristic and its future expected evolution underlines the long-term efforts that still have to be put on this field.

Existing or under development products / services[58]

Oncology:

- Angiogenesis inhibiting protein SB101
- Inhibitors of Wnt, AKT and p53 pathways
- Tumour cell specific growth inhibitor
- Antibodies against cancer cell gene expression patterns
- Vaccine combination against genetic melanoma using plant virus-derived virus like particles (VLPs)
- Oligonucleotides as anti-cancer drugs
- NK cells for immunotherapy

CNS

- Antagonists for binding to the D2 receptor and neurotensin analogs as precursor drug candidates to treat schizophrenia

Infection diseases

- DNA vaccination against HIV

Regenerative medicine:

- Differentiation of mesenchyme cells for autologous transplantations

Examples of companies involved in the therapeutic development field[59]

Endogenous companies:

- Celecure AS: Celecure AS does drug discovery and development of novel anticancer drugs. Celecure is the research and development unit of Celecure Group, the leading Estonian biotech company with the aim to become a leading player in global anticancer drug development market. There are currently two drug candidates/technologies in the pipeline: SB101, an angiogenesis inhibitor to treat solid tumours (less than 1 year to clinical studies) and, according to the company's website, ENTRYBODY™, a new platform technology to target and block intracellular disease-related molecules.
- Kinasera: Kinasera is a biotechnology start-up, founded in 2006 as a spin-off of the University of Tartu. It develops and commercializes novel inhibitors of protein kinases (PK) and assay technologies for screening and characterization inhibitors of PK. New biological tools provided by the company rely on the high-affinity bisubstrate-analog inhibitors of PK and constitute fluorescent probes and affinity adsorbents for HTS assays and other methods of analysis of the proteome.
- InBio OÜ: InBio is a supplier of laboratory equipment created in 1999. InBio commercializes products from Becton Dickinson Biosciences, Invitrogen, Génome, Leica Microsystems, Bruker Daltonics, Thermo Scientific NanoDrop, ESCO, Sigma Laborzentrifugen, Tuttnauer, Nouveau-Brunswick, Amresco, Deltalab and Unigloves.
- ProtoBios AS: Protobios is developing several techniques to isolate and propagate tissue-specific stem and progenitor cells. First Protobios has developed a technology to transdifferentiate non-neuronal cells into neural stem/progenitor cells by using manipulation of culture conditions. Second, Protobios has developed a technology that is based on the transient manipulation of cellular signalling systems and transcription factors to reprogram cellular regulatory mechanisms.
- Kevelt AS: Kevelt is a CMO engaged in the production of sterile pharmaceuticals and bioactive eicosanoids for scientific purposes.
- Bestenbalt LLC: Bestenbalt LLC is a privately held manufacturing biotechnology company that specializes in production of recombinant and natural proteins, peptides, and their derivatives.
- LabAs Ltd.: LabAs Ltd. was established in 1991 in Tartu, Estonia as a private company by specialists in the fields of immunology, immunochemistry, protein chemistry and purification, cell biology, genetics, human and veterinary medicine. They have about 20 years of experience in producing, purifying and labelling of mono- and polyclonal (mouse, goat, rabbit, chicken) antibodies.
- Molcode Ltd.: The main activity of the CRO MolCode is the development of the technology and software, holding the intellectual property and providing the services and contract research on the computational prediction of the properties of chemical compounds and materials and on the prediction of compounds and materials with predetermined properties.
- Quattromed AS: Quattromed Ltd is one of the leading biotechnology companies in Estonia providing medical diagnostics services and performing custom research programs for the biopharmaceutical industry. As of 2 March 2009, Icosagen AS is the new business name of the former Quattromed Ltd. Quattromed was established in 1999 as a spin-off from University of Tartu, with 80 full-time employees in 2009. Quattromed started with offering molecular diagnostic services, the activities today cover molecular and clinical diagnostics (Quattromed HTI Laboratories), life science products (Quattromed), latex allergen testing (Quattromed Ltd) and protein production (Quattromed Cell Factory).

58 Interviews
59 http://www.estonianbiotech.com

Exogenous companies:

- ProSyntest AS now Cambrex Tallinn: ProSyntest is a provider of custom organic synthesis and contract research and development for the pharmaceutical and fine chemical industry, with a focus on customer needs in quality, confidentiality, in-time delivery and cost efficiency.
- EGeen: EGeen is a transatlantic CRO, subsidiary of EGeen Inc. USA California, whose key business focus is to advance the drug development of biotech and pharmaceutical clients via expeditious and high quality yet cost-effective clinical trials.
- Applied Phenomics LLC is a privately held clinical genomics company, which specializes in gene expression profiling and target validation products and services, and in pathology support services for clinical trials.
- Nycomed Sefa AS: a subsidiary of Nycomed International Management GmbH, Switzerland. Nycomed is engaged in all aspects of a product's life, from research and development to customer relations. With a broad portfolio of products and a powerful pipeline, they work in a wide range of therapeutic areas, particularly cardiology, gastroenterology, osteoporosis, respiratory, and pain and tissue management.
- PharmaSwiss – Estonia: PharmaSwiss SA is a medium-sized pharmaceutical company. Established in Switzerland in 2000, PharmaSwiss handles an entire piece of business that is logistically and financially impractical for companies whose strategic focus is elsewhere in the world. They form exclusive, long-term partnerships with research-based pharmaceutical MNCs and Biotechs, as well as hospitals, clinics, doctors and pharmacies.

Celecure has developed two patent families and in-license an exclusive global license from Swedish company Angitia AB to develop the innovative anti angiogenesis inhibitor SB101.[60]

Two VCs have invested in Estonian therapeutic development companies:

- Celecure AS has an investment from ASI Ltd, an investment company of the founders of Skype
- Quattromed HTI Ltd. has an investment from Baltcap (www.baltcap.com). Baltcap is a classic generalist equity fund.

Supporting Research and Development for the Field

Therapeutic business field can rely on a strong support from academic and institutional research and development but lacking the critical specialized industrial property skills in house, in universities and institutions leading to a rather limited number of filed patent applications. In addition to that there are limited efficient specialized Technology Transfer Offices in the field with business development teams at international biotech and pharmaceutical standards for out-licensing purposes with the worldwide biotech or pharma industry.

Besides having a good critical mass of health biotech industry, Estonia can also rely on a good critical mass of institutions and universities working in the field of therapeutic development and able to support the industry if valorisation and technology transfer were organized according to international standards:

Department of Biomedical Engineering of Tallinn University of Technology: the mission of the Institute of Bioengineering is to be the leading institution for the interdisciplinary area of biomedical equal partner in Estonia and in the world, which carries out a high level of research and high-quality teaching at different levels.

Institute of Molecular and Cell Biology, University of Tartu

Estonian Biocentre: The Estonian Biocentre (EBC) was established in 1986 by the decree of the government as a joint venture between University of Tartu and the Institute of Chemical Physics and Biophysics to promote research and technological development (RTD) of gene and cell technologies in Estonia. It is an independent public research institute reporting to the Ministry of Education and a Centre of Excellence since 2000. EBC has currently a project named ECOGENE with the first objective lying in the networking of the Estonian Biocentre with centres of research excellence in the EU via joint research and training activities, including exchange of students and research personnel and a second objective addressing human capital building for research and development in genomics, in order to meet the needs of the opening of Estonian Biobank Project to the proposed under ESFRI European Biobank program.

Estonian University of Life Sciences: Estonian University of Life Sciences is the only university in Estonia whose priorities in academic and research activities provide the sustainable development of natural resources necessary for the existence of Man as well as the preservation of heritage and habitat.

60 Celecure wabsite, 2004

Institute of Gene Technology of Tallinn University of Technology

Competence Center for Cancer Research: Founded in 2005 by a consortium of eight partners (TUT, North Estonia Medical Centre (NEMC), Trial Form Support (TFS), CeMines Estonia Ltd, Cambrex Tallinn Ltd, Kevelt Ltd, Celecure Ltd and Inbio Ltd), its aim is to improve the quality of cancer therapy by developing and implementing new diagnostic platforms and offering the pharmaceutical industry new cancer drug candidates. Other organizations, such as the University of Tartu (UT), ProtoBios Ltd., EPhaG Ltd., Quattromed HTI Laborid Ltd. and Baltic Technology Development are also involved in its work. Currently the project portfolio of CCCR involves 7 projects in drug development and 3 in diagnostics, among which:

- Identification and characterization of inhibitors of the Wnt, AKT and p53 pathways
- Development of SB101, an angiogenesis inhibiting protein currently in preclinical development
- Soluble recombinant fragment of human protein CD44, novel class of angiogenesis inhibitors at preclinical stage
- Development of antibodies against cancer cell gene expression patterns focused on lung, prostate and breast cancer
- Protein vaccine – Potato A potyvirus PVA CP VLPs against genetic melanoma
- Novel chemically modified oligonucleotides as anti-cancer drugs
- Cellular Immunotherapy by transferring NK cells prior to stem cell transplantation

Center of the excellence for the translational research (CETR):

This centre is dedicated to metabolic diseases (diabetes), autoimmune disorders, rodent and non-rodent animal models, molecular imaging for in vivo in animal imaging. This centre is also focused on clinical biomarkers discovery, pharmacogenomics and early clinical phases (Phases 0 and I in addition to preclinical phase). The model adopted by the centre of excellence is to develop molecules up to regulatory preclinical or phase I depending of the financing situation. Five projects have been identified:

- Novel target identification for type II diabetes
- Novel anxiolytic drug that has been patented
- 2 novel targets for psoriasis with the purpose of local treatment shortening the time for development
- Reliable database for patients suffering from neurodegenerative diseases and in particular Parkinson disease
- Molecular epidemiology study correlating phenotypes and genotypes within HIV patients

Center of excellence for endothelial research (CEER): the centre covers both therapeutic and diagnostic development in both CV and oncology therapeutic areas.

This critical mass of academic research is also reinforced by the same Estonian key opinion leaders at international levels: Pr. Koks, Pr. Salumet, Pr. Neumann, Pr. Ustav.

Interviews led to the identification of structuring equipment for manufacturing purposes. Although small-scale GMP batches currently exist in Estonia, mid-size GMP pilot is still missing leading to difficulties in producing the necessary amount of biological.

Summary

A high added value long-term research and development opportunity for Estonia if only dedicated to cutting edge innovative class of products:

Strengths ■ A critical mass in therapeutic development both endogenous and exogenous to rely on for in-licensing opportunities and research and development. ■ A critical mass in the academic research and development with one competence centre (CCCR) and a couple of the universities with specialized departments and institutions and two centres of excellence (CETR and CEEC). ■ Early stage portfolio of the patent applications. ■ Highly qualified research and development workforce (publications in peer review journals). ■ A couple of internationally recognized Key Opinion Leaders. ■ A critical mass of project submitted for grants and funding.	**Weaknesses** ■ Limited number of patent filed. ■ Lack of industrial property skills (patent filing, prosecution, litigation) to further support academic researchers. ■ Limited number of PhD. ■ Limited number of therapeutic development skills. ■ Lack of dedicated therapeutic development-specialized VC (with good understanding of correlated timelines and ROI). ■ Lack of investment. ■ Lack of structuring equipment available for the industry under industrial standard conditions (contractual conditions, confidentiality, safety): e.g. manufacturing plant. ■ Lack of specialized TTO used to support therapeutic development project maturation. ■ Limited critical mass in infectious diseases leading to an outcome going through international collaboration and valorisation.
Opportunities ■ A global appetite of Big-pharma for innovative and new class of molecules and biomolecules to replace their loss of patent products whatever the therapeutic area. ■ An opportunity for Estonian biotech companies, mainly focused on the services, slightly to move to a mix model of service and early therapeutic development of product to increase the value of the company and build long-term business field. ■ A couple of therapeutic areas with still major unmet needs (oncology: colorectal cancer, pancreas cancer, bladder cancer, renal cancer). ■ A niche opportunity around reproductive medicine to explore further under a loco-regional market (Estonia, Baltic countries, proximal Russia). ■ The development of structuring equipment: mid-size GMP pilot plant. ■ The creation of a Medical/Life Science council to prioritize health science subject. ■ A strong political support for the in vivo in animal imaging centre to help becoming the National centre and a model for academia and industry as well as for Baltic and Scandinavia.	**Threats** ■ Industrial patent policy, new research and development projects, new endogenous company, and innovation need to be much more supported (financially) in Estonia to compete at international level. ■ Huge and highly active competition in therapeutic development in oncology with both major pharma and innovative biotech (and in particular for tyrosine kinase inhibitors leading to limited possibility of success except in the case of a cutting edge class of molecules that could in that case benefit from the big-pharma appetite for this topic). ■ High-density competition for CNS disease solutions with a lot of efforts for neurodegenerative disorders. ■ Strong competition in the inflammatory and autoimmune field with complex clinical development. ■ No room available for "me too" or even "me better" products on these highly competitive markets.

Conclusion about the Potential for Estonia

Therapeutic development is a potent, high added value but long-term opportunity for Estonia. Taking into account the huge and highly active competition in this field as well as the long time to market (4 to 9 years for early development, meaning up to end of preclinical phases), major efforts should be put into cutting edge innovative class of products as the competitive pressure is even stronger for "me too" or "me better" product with no real possibility to emerge in such environment.

However, this field represents an opportunity for Estonian biotech companies mainly focused on services to evolve towards a mix model of service and early therapeutic development of product as a solution to set up a sustainable long-term business field.

A niche opportunity around reproductive medicine has to be further explored for locoregional market opportunity.

Structuring equipment, such as mid-size GMP pilot plant could catalyze the field as upstream, downstream processes and manufacturing in general remains an underestimated topics by most biotech companies leading to additional unacceptable delays in the development.

The creation of a Medical/Life Science council would certainly help structuring the whole healthcare field with the aim to prioritize health science subjects.

A strong political support for the in vivo in animal imaging centre to help becoming the national centre and a model for the academia and industry, as well as for Baltic and Scandinavia would certainly be a good sign for motivation of health players (researchers, industrials, students, foreign collaborators).

1.6.2 Diagnostics

Introduction[61]

Definition of the Field
Molecular Diagnostics (MDx) is defined as a subdivision of the in vitro diagnostic (IVD) market. MDx tests investigate the molecular basis (study of DNA, RNA, proteins) of metabolic pathways, disease development and link the results to drug targets and metabolism.

The MDx market can be split into:
- nucleic acid testing (NAT) for blood banking
- viral load/genotype testing
- sexually transmitted disease/infectious disease testing
- genetic testing and
- industrial testing (covering food, water, beverage and personal care)

Biomarkers are defined as "measurable characteristics that reflect physiological, pharmacological or disease processes in animals or humans" by the regulators. Changes in biomarkers following treatment reflect the clinical response to the product. Techniques as disparate as imaging, serum or genetic assays or psychological tests can yield biomarkers that are useful in product development.

Key applications of biomarkers as molecular diagnostics area are[62]:
- Diagnostic (Screening) Biomarker: a marker that is used to detect and identify a given type of disease in an individual. These markers are expected to have high specificity and sensitivity.
- Prognostic Biomarker: a marker that is used once the disease status has been established. These biomarkers are expected to predict the probable course of the disease including its recurrence, and they therefore have an important influence on the aggressiveness of therapy
- Stratification (Predictive) Biomarker: a marker that serves to predict the response to a drug before treatment is started. This marker classifies individuals as likely responders or non-responders to a particular treatment.

A biomarker is defined as a characteristic that is qualitatively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention. Regulators and researchers believe that the identification, characterization and validation of biomarkers may be used to develop tailored medicine which can target specific individuals and lead to personalized therapies. Nowhere is this more apparent than in the field of oncology, where there is often a defined genetic, proteomic or metabolic component which influences an individual's susceptibility to disease or response to therapy. The bi-directional approach to drug discovery and development, so-called translational research and broadly covered in the section Therapeutic business field, has resulted in the identification of biomarkers – measurable molecules in the human body that can be correlated with a disease or can provide a measure of the impact of a drug (e.g. toxic or adverse effects).

61 *Molecular Diagnostics: a primer on an emerging sector*, Datamonitor, 11/2008.
62 *Cancer, CNS & Cardiovascular Biomarkers: Players, products and prospects*, Espicom, 2008

Examples of Products and Services
There are many types of biomarkers:

- Drug activity biomarkers, such as pharmacodynamic (PD) or pharmacokinetic (PK) biomarkers to help researchers understand the mechanism of action of a drug;
- Toxicity biomarkers to help researchers understand and develop dosage parameters to determine at which point a drug will be toxic to a patient;
- Disease biomarkers that help researchers understand the pathology of a disease for diagnosis and prognosis;
- And Predictive biomarkers from molecular profiling of samples to identify biomarkers that will translate into predictive clinical markers.

Biomarkers may be identified through genomics (mRNA, DNA, SNPs, methylation), proteomics (amino acids, proteins), metabolomics (metabolites), transcriptomics and autoantibodies from a variety of biological fluids (blood, plasma, serum, saliva), tissue biopsies, hair follicles, skin as well as imaging and electrophysiology readouts.

The industry is migrating from a single source biomarker to multiple source biomarker profiles or signatures.

Large numbers of companies, such as Roche Diagnostics, Quest Diagnostics, Abbott Diagnostics, Epigenomics, Genzyme Genetics etc have developed or commercialized biomarker kits, tests and diagnostics (IVD) and the industry has recognized the potential of biomarkers to guide research and development programs.

A variety of technology platforms, such as: immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR), micro- and nanoarrays, mass spectrometry and imaging technologies have been utilized in biomarker discovery, identification and validation. At early stages of development, this diagnostic business field overlaps the drug discovery business field in terms of the enabling technologies required to identify and characterize biomarkers.

Technology and service providers have become established to enable the pharmaceutical and diagnostic industries to tap into specialist technologies and "skill sets" as and when required in order to run internal and external biomarker programs.

Within personalized medicine, synergy between prescription pharmaceuticals and molecular diagnostic tests has been identified and referred to as 'companion diagnostics'. There are at least five targeted oncology therapies which look set to drive the molecular diagnostics movement over the coming six years (due to the need of accurate diagnostic testing):

- Genentech/Roche's Herceptin (trastuzumab),
- Novartis's Glivec (imatinib)
- Bristol Myers Squibb's (BMS)
- Sprycel (dasatinib)
- BMS/Merck KGaA's Erbitux (cetuximab)
- Amgen's Vectibix(panitumumab).

Additionally, there are two therapeutics outside of the oncology arena which are accompanied by MDx tests of significant importance: Pfizer's recently launched Selzentry (maraviroc) for HIV and Bristol Myers Squibb's Coumadin (warfarin) a leading anticoagulant.

Cancer biomarkers:
A known valid biomarker is a biomarker that is measured in an analytical test system with well established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic or clinical significance of the results. The following biomarkers exists: CA 15.3, Her-2 gene expression, TRUQUANT BR for breast cancer, BCR-ABL mutation for Chronic myeloid leukaemia, CEA and EGFR expression for colorectal cancers, C-kit expression for gastrointestinal stromal tumours, PSA for prostate cancer.

CNS biomarkers:
The diagnosis of CNS disorders is often complex and requires the assessment of symptoms, signs and medical history with the medical profession to diagnose an illness. There are no laboratory tests available to help diagnose many CNS and imaging technologies, such as radiographic computed tomography (CT) and magnetic resonance imaging (MRI) may be used to confirm diagnosis by providing a detailed anatomical and functional map of the CNS. Although several neuroimaging and circuitry-based diagnostics are being evaluated for CNS disorders, such as ADHD, substance dependence, depression, schizophrenia, and obsessive-compulsive disorder, there continues to be a need for better contrast agents to increase sensitivity.

There are currently no diagnostic biomarkers for neuropyschiatric illnesses and neurodegenerative diseases; nor is the underlying aetiology of these disease processes well understood.
The only CNS biomarker success story is Curidium's recently approved PsychINDx which uses a panel of biomarkers to stratify schizophrenic patients into four groups that may respond to different classes of anti-psychotics.

Cardiovascular (CV) biomarkers:
A number of CV biomarkers have been clinically validated and are commercially available for diagnostic testing, such as B-type natriuretic peptide (BNP), N-terminal proBNP, Troponin I (TnI) or Troponin-T(TnT), Creatine kinase MB isoenzymes (CK-MB), Myoglobin, Ischaemia modified albumin (IMA) and Myeloperoxidase (MPO) for Acute coronary syndromes, C-reactive protein (CRP) and high sensitivity-CRP (hs-CRP) or Apolipoprotein A and B (ApoA, ApoB) for CV risk, Lipoprotein-associated phospholipase A2 (Lp-PLA2) or Homocysteine for CV and stroke risk, D-Dimer or Prothrombin Factor II for thrombosis, Protein C deficiencies for Warfarin administration.

International Business Potential

International Market Size and Growth
Pharmaceutical sales have continued to rise steadily during the last five years, generating over US$675 billion in 2007, and are expected to experience single digit growth over the next five years. Research and development costs are escalating dramatically and the number of approved new drug products has declined with only one out of ten experimental drugs succeeding in clinical studies. The industry is constantly searching for new ways and technologies to expedite the drug discovery process which is under constrained research and development budgets. Biomarkers and molecular diagnostics may provide one answer to this problem.

According to industry analysts, the global market for biomarkers is forecast to grow from over U$5.6 billion in 2007. The forecast expects a growth up to just under US$11.6 billion by 2012, with a compound average growth rate (CAGR) of 16.0% as biomarkers are applied increasingly to a variety of therapy areas and numerous biomarkers become validated for use in clinical trials and finally for in vitro diagnostics.

Revenue from biomarkers can be subdivided into three main segments:
- biomarker discovery – for applications in drug discovery, preclinical studies of drug development and diagnostics research;
- clinical trials – biomarkers for use as surrogate endpoints to aid go/no go decisions in clinical trial design; and
- molecular diagnostics –PoC and laboratory-based diagnostic tools to guide the prescription of products, i.e. helping to choose the right drug for the disease and the patient.

The second largest segment in terms of revenue (after the biomarker discovery segment) is molecular diagnostics, which was estimated to be worth US$2.3 billion in 2007, representing 41% of all biomarkers revenues and is forecasted to rise to over US$4.6 billion by 2012 (CAGR of 15.0%).

CNS biomarker market currently accounted for less than 5% of biomarker revenues to generate over US$150 million with the majority of revenues derived from biomarker discovery in schizophrenia and neurodegenerative disorders.

The total global in vitro diagnostic (IVD) market was estimated to be US$39 billion in 2007. The IVD market is forecast to increase at a 2007–13 CAGR of 5.0%, to a figure in excess of US$52 billion by 2013. The historically small, but fast-growing MDx market is forecast to continue this trend, with a 2007–13 CAGR estimated at 14.0%.

Trends and Developments[63]
By 2015 the biomarker market is forecast to be worth over US$20 billion as the cardiovascular and CNS biomarker market segments begin to mature with the launch of a number of diagnostic tests to guide the treatment of neuropsychiatric and neurodegenerative diseases (Figure 13).

63 *Molecular Diagnostics: a primer on an emerging sector*, Datamonitor, 11/2008

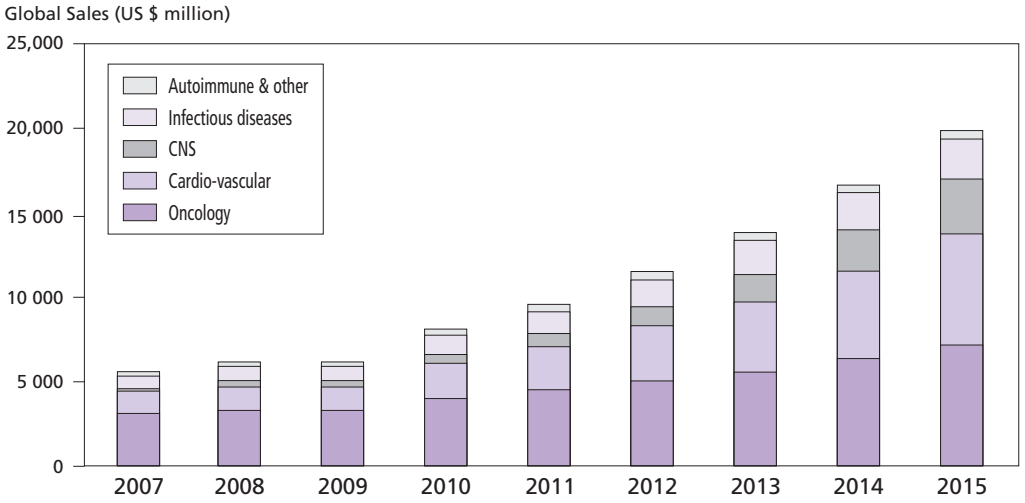


Figure 13: Growth in biomarker market 2007–2015 (USD millions)

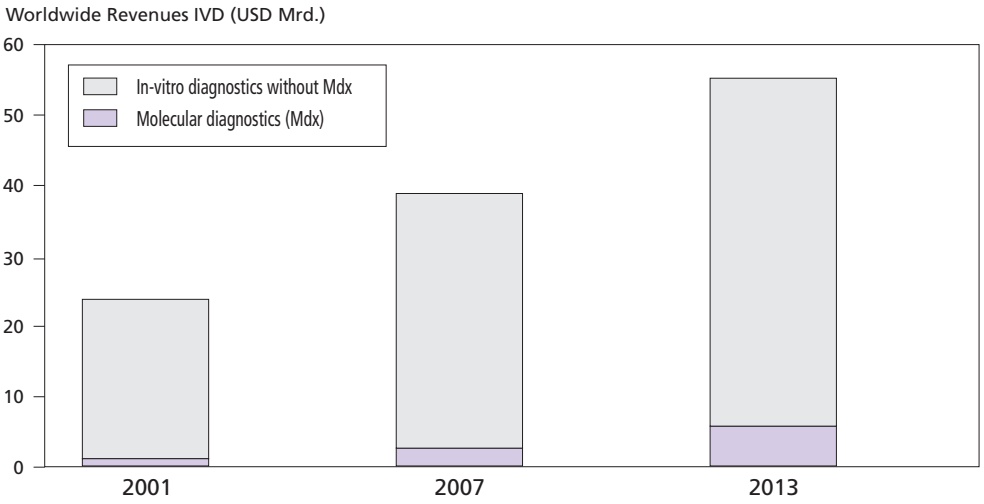


Figure 14: Worldwide Revenues IVD (USD bln)

This dramatic growth is reflected by the influx of biomarker specialist companies and growth in service and technology providers, initially in oncology, cardiovascular disease, CNS disorders and infectious diseases and latterly in autoimmune diseases. However, many challenges still need to be overcome, not least the establishment of regulatory guidelines, the standardization of biomarker data and protocols and qualification/validation of surrogate end-points including genomic, proteomic and metabolomic biomarker profiles, imaging technologies and electrophysiology read-outs.

The strong sales forecast of targeted therapies and personalized medicine, such as the monoclonal antibodies Herceptin (trastuzumab) and Erbitux (cetuximab), the tyrosine kinase inhibitors Gleevec (imatinib), Sprycel (dasatinib) in addition to new fist-in-class therapies, such as Pfizer's Selzentry (maraviroc) for CCR5-tropic HIV, is also driving sales growth of the MDx market. These therapies have accompanying diagnostic tests, some of which have to be performed on the patient in order to obtain the treatment, thus adding further sales growth impetus into this developing market segment.

The biomarker market is driven by:

- growth in biomarker therapies outside cancer, such as CNS and cardiovascular disease; investment in biomarker discovery and alliances with specialists;
- the launch of new targeted therapies that may require a diagnostic to guide treatment – helping to stratify patients and choice of treatment, dose and regimen;

- routine use of biomarkers in research and development programs and greater submission of biomarker information during drug filing;
- inclusion on drug labels and support for the reimbursement of diagnostic tests, which will catalyze further investment in this dynamic market;
- increased availability of diagnostics and reimbursement of tests to encourage greater use earlier in the treatment process;
- a shift in the healthcare system towards proactive testing rather than reactive testing which is expected to drive growth in IVDs as tests aim to provide patients with better treatment outcomes, safer treatments and more cost-effective healthcare.

Cancer biomarkers[64]:
A probable valid biomarker is a biomarker that has not reached the status of a known valid marker because the data elucidating its significance, although highly suggestive, may not be conclusive. Probable cancer biomarkers include APC or P53 for colorectal cancer, PCA3 for prostate cancer.

In addition, there are a vast number of "possible" biomarkers that have been identified by academic institutes which require further validation to determine their potential as markers of disease or therapeutic response. Possible cancer biomarkers include angiogenin or osteopontin for bladder cancer, methylation of vimentin gene for colon cancer.

CNS biomarkers:
CNS diseases and disorders represent the largest and fastest growing area of unmet medical need: 1.5 billion people worldwide, including over 100 million people in the US, suffer from CNS diseases or disorders. According to the World Health Organization (WHO) mental illness affects one in three people and depression will be the second largest healthcare burden by 2020, ahead of cancer.

Many CNS therapies are under clinical evaluation that targets the underlying cause of the disease and not just the symptoms of the disorder, and companies are searching for biomarkers that may aid drug development and treatment in conditions, such as neurodegenerative and neuropsychiatric disorders.

Two of the most widely known and researched neurodegenerative CNS biomarkers are: tau and abnormally phosphorylated tau (p-tau) proteins which strongly correlate with Alzheimer's disease (AD) and disease progression (increased levels of p-tau are associated with a poorer prognosis). Applied NeuroSolutions are developing a CSF test using p-tau 231.

In addition, there are a vast number of "possible" biomarkers that have been identified by academic institutes which require further validation to determine their potential as markers of disease or therapeutic response. A couple of probable and possible CNS biomarkers (DNA, protein and metabolic markers) that have been identified by academic institutes and the industry during the last five years: Serum Gene GFAP (glial fibrillary acidic protein) or Osetopontin biomarker for Alzheimer disease; plasma alpha-1-antitrypsin for Parkinson disease; CSF2RA and IL3RA genes for Schizophrenia.

Important International Market Participants[65]
- Roche is the dominant player in the MDx field, with a 20% market share, equating to 2007 MDs sales of US$984 million.
- There are nine leading MDx companies, with a combined market share totalling 95% of the total MDx market in 2007; Roche Molecular, Gen Probe, Abbott Molecular, Myriad,Siemens, Becton Dickinson, bioMerieux, Qiagen and Third WaveTechnologies (now part of Hologic).

Specific major players within the cancer biomarkers[66] firms include Abbott Diagnostics, Affymetrix, Beckman Coulter, Biomedical Diagnostics, Caprion Proteomics, Dako Denmark A/S, Epigenomics AG, Genzyme Genetics, Ipsogen Therapeutics,

CNS biomarkers players are mainly at the stage of probable biomarkers with for instance Applied NeuroSolutions, Nanogen, Inc., Satoris, Inc., DigiLab, Inc. for Alzheimer biomarkers, Osta Biotechnologies for Parkinson biomarkers and Clinical Data, Inc. for schizophrenia. Possible biomarkers are essentially developed in academic environment (USA, UK, Israel, Ireland, France) but also in companies, such as Pfizer, Aegera Therapeutics, Biogen Idec, Astra-Zeneca.

64 *Cancer, CNS & Cardiovascular Biomarkers: Players, products and prospects*, Espicom, 2008
65 *Molecular Diagnostics: a primer on an emerging sector*, Datamonitor, 11/2008
66 *Cancer, CNS & Cardiovascular Biomarkers: Players, products and prospects*, Espicom, 2008

Cardiovascular biomarkers players include Abbott Diagnostics, Inverness Medical Innovations, Siemens Medical Solutions, Diagenics International Corporation, Beckman Coulter, ARCA Biopharma, LabCorp.

Time to Market
The time to develop a biomarker is currently estimated between 5 to 10 years, depending on the type of biomarker (discovery, molecular diagnostic or clinical trials), the complexity of the signature and the required clinical validation. [67]

However, the time to market for the enabling technologies aiming at facilitating the discovery and the development of biomarkers, subject broadly covered in the section drug discovery, can have much shorter timelines.

Identified Bottlenecks
In order for companies in the biomarker market to meet the challenges facing them, it will be necessary:
- to provide and adopt a fully integrated and multifunctional approach to biomarker discovery and development;
- to reinforce IP regulation to prevent competition and drive innovation within the market;
- to further develop technologies necessary for biomarker discovery and validation to continue;
- to solve the issue of the number of patients to include in clinical trial validation, number which is usually underestimated leading to failure in the development;
- to standardize biomarker data and imaging protocols;
- to solve the issue of reimbursement for expensive new treatments that may stifle growth to be addressed;
- and to get financial investment to discover, identify and clinically validate biomarkers for diagnostic use.

Some specific challenges have to be overcome for CNS biomarkers:
- The complexities of the central nervous system which may be associated with over 1,000 different disorders
- The level of understanding of the genetic and proteomic components of these disorders for biomarker selection
- The difficulties associated with crossing the blood brain barrier and the unique microenvironment in which the CNS is located;
- The weight of the regulatory evaluation and qualification process for CNS biomarker submissions
- The need to develop tools and technology platforms to aid CNS biomarker discovery and validation and bioinformatics to analyze large amounts of data rapidly and efficiently.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation
The Estonian diagnostic industry field is mainly based on small companies with less than 50 employees, very similarly to the therapeutic development business field. As in the whole health business field, the Estonian diagnostic industry market is mostly dominated by endogenous companies with about 10 companies, as well as a couple of exogenous companies. This pool of companies definitely represents a real industry critical mass and a leading business field.

The early stage of development of the health biotech business industry in Estonia as well as the lack of patent filing use are consistent with the most commonly found services business model. Although services business model allows relatively quick time to market and launch the products and services, limited economic return and low company value are often correlated with. In order to develop a sustainable business field, all the challenge will be to move from a services-focused model with very few industrial property towards a product-oriented model (which can also include services to continue generating turnover) with strong industrial property portfolio in order to allow the proper development of biomarkers, signatures, associated data management tools.

Examples of companies involved in the diagnostic field
Beside health endogenous companies that have already been described in the section therapeutic business field because deeply involved in both fields for healthcare product and services development in general, a couple of companies are particularly dedicated to diagnostic:
- Asper Biotech AS: Asper Biotech, founded in 1999, offers DNA tests for the diagnosis of over fifteen different human diseases to healthcare professionals worldwide with 17 genetic tests on the market with sales rate growing every year. The company also provides custom genotyping projects and genetic testing hardware to the scientific and commercial communities. Asper employs over 40 people among them scientists, technical personnel, and management.

67 Ernst & Young internal experts & knowledge

- Quattromed AS: Quattromed Ltd is one of the leading biotechnology companies in Estonia providing medical diagnostics services and performing custom research programs for the biopharmaceutical industry. As of 2 March 2009, Icosagen AS is the new business name of the former Quattromed Ltd. Quattromed was established in 1999 as a spin-off from University of Tartu. It is based in Tartu, Estonia, with 80 full-time employees. Quattromed started with offering molecular diagnostic services, the activities today cover molecular and clinical diagnostics (Quattromed HTI Laboratories), life science products (Quattromed), latex allergen testing (Quattromed Ltd) and protein production (Quattromed Cell Factory).
- Docobo Ltd: The company has developed a remote monitoring service for LTC's, called doc@HOME®, and is developing a focused range of related services and products to expand its portfolio. This Telehealth service offers care providers with an integrated low cost solution for the collection, management and analysis of essential patient related data, and permits efficient interaction between clinicians and patients at home.
- FibroTX Ltd.: FibroTx is focused on personalized medicine and cosmetics, and on drug development in the area of stromal cell (connective tissue) related health and cosmetic problems. FibroTx is developing diagnostic tests and drugs to monitor and control function of connective tissue cells as well as structure and function of extracellular matrix (ECM). FibroTx skin care and clinical tests are based on the genomics, proteomics and systems biology of stromal cells.
- Immunotron: The aim of the company is to develop novel immunodiagnostic devices for human diseases. The company is performing measurements of antibodies etc. in serum/plasma samples of diverse origin.
- Labema Eesti Ltd.: As a specialized company Labema Oy has established a leading position as a provider of diagnostic products and reagents for microbiological laboratories in Finland and Estonia. Labema Oy's clients include all the significant food control laboratories, clinical laboratories, research centres, universities, and food or other industries involved in microbiological diagnostics in these countries.
- Medisoft: Medisoft is one of the largest suppliers of software development and related ITC services in the field of social insurance and healthcare in Estonia and Baltic States. Main areas of activity of Medisoft are system analysis, design and development of information systems, system integration, consulting, end-user training and technical support.
- OÜ TorroSen: TorroSen OÜ is a spin-off company, commercialising the new technology of biosensors.
- Pharmasynth AS: PharmaSynth AS produces sophisticated organic molecules, which are mostly used as precursors and reference standards for Positron Emission Tomography (PET), a medical diagnostic method that is unique in its ability to image molecular processes in human patients and thus show even minor functional changes in human body.

Exogenous companies:
A couple of exogenous companies are also developing diagnostic products or services, such as:

- EGeen: EGeen is a transatlantic CRO, subsidiary of EGeen Inc. USA California, whose key business focus is to advance the drug development of biotech and pharmaceutical clients via expeditious and high quality yet cost-effective clinical trials.
- Cemines Estonia: CeMines, subsidiary of CeMines Inc, was founded in 2000 to develop cancer diagnostics using two methods: autoantibody and splice variant technologies.
- Applied Phenomics LLC is a privately held clinical genomics company, which specializes in gene expression profiling and target validation products and services, and in pathology support services for clinical trials.

Licensing activities:
This diagnostic business field in oncology has already led to a licensing agreement between CeMines and Ortho Clinical Diagnostics for CeMines' lung cancer industrial property in December 2008. CeMines, Inc., a developer of innovative solutions for early stage detection of cancer, today announced it has entered into an exclusive agreement with Raritan, N.J., based Ortho Clinical Diagnostics ("OCD") to license certain CeMines Intellectual Property relating to blood based testing for early stage lung cancer. CeMines' test, based on proprietary IP, has shown a significant increase in the ability to detect early stage lung cancer compared to other known approaches. Studies are currently underway to finalize validation.

Industrial property status:
A couple of patent applications are currently emerging showing the best practices to further follow in order to move towards sustainable economic return. Recent patent filing included patent applications on dermal biomarkers and the way to detect them (5 patent applications among which 2 to 3 are published) as well as 4 patent applications on mRNA splice variants owned by CeMines about:

- Methods and compositions for the diagnosis, prognosis and treatment of cancer; Owner: CEMINES INC; Authors: Kaia Palm, Toomas Neuman, Daiwei Shen; Priority number: US20040584784P; Priority date: 30.06.2004

- Mammalian neuralized family transcriptional regulators and uses; Owner: CEMINES INC; Authors: Kaia Palm, Tõnis Timmusk; Priority number: US20010808387; Priority date: 14.03.2001
- Methods and compositions for the diagnosis, prognosis, and treatment of cancer; Owner: CEMINES LLC; Authors: Kaia Palm, Toomas Neuman; Priority number: US20020436693P; US20030746547; Priority date: 26.12.2002
- Profiling tumour specific markers for the diagnosis and treatment of neoplastic disease; Owner: CEMINES LLC; Authors: Kaia Palm; Priority number: US20000249508P; Priority date: 16.11.2000

This challenge around industrial property raises the following issue: taking into account the limited financial resources available in Estonia as well as the limited available skills to file patent applications, the very point remains when should a patent application be filed? This question should be closely related with the capacity to develop the right and required proof of concept otherwise no license will ever be possible.

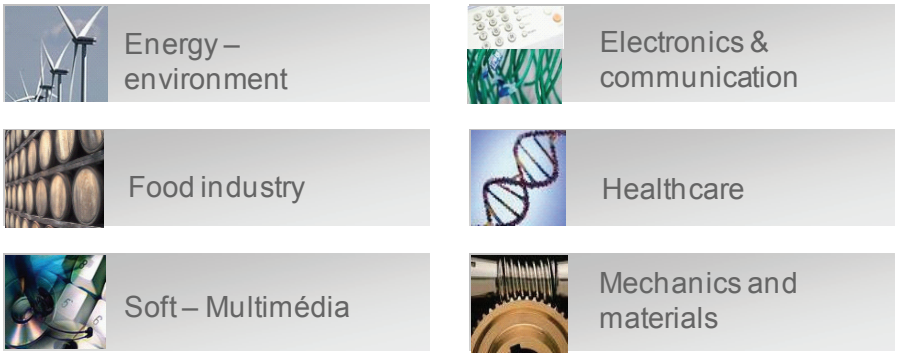
Benchmark on best practices in terms of project appraisals for improvement of industrial property position and technology maturation:
Both in Europe and in North America, biotech industry and academia have worked together to improve the academic capacity to protect their innovation and manage to develop it enough to allow the industry to in-license it from there and develop it further for mutual benefit. A couple of tools have been created to help, secure and even finance the maturation and the evolution of the early technology:

	Examples of programs / actions / steps
Innovating research projects	Emergence Bio (France), National competition for the creation of innovating companies (France)
Research valorisation	VIB (Belgium), VTT (Finland),Karolinska Institute (Sweden)
Financing of private and public research	National competition for the creation of innovating companies (France)
Technology transfert	VIB (Belgium)
Creation of necessary tools for the scientific and technological development	Genome (Québec)

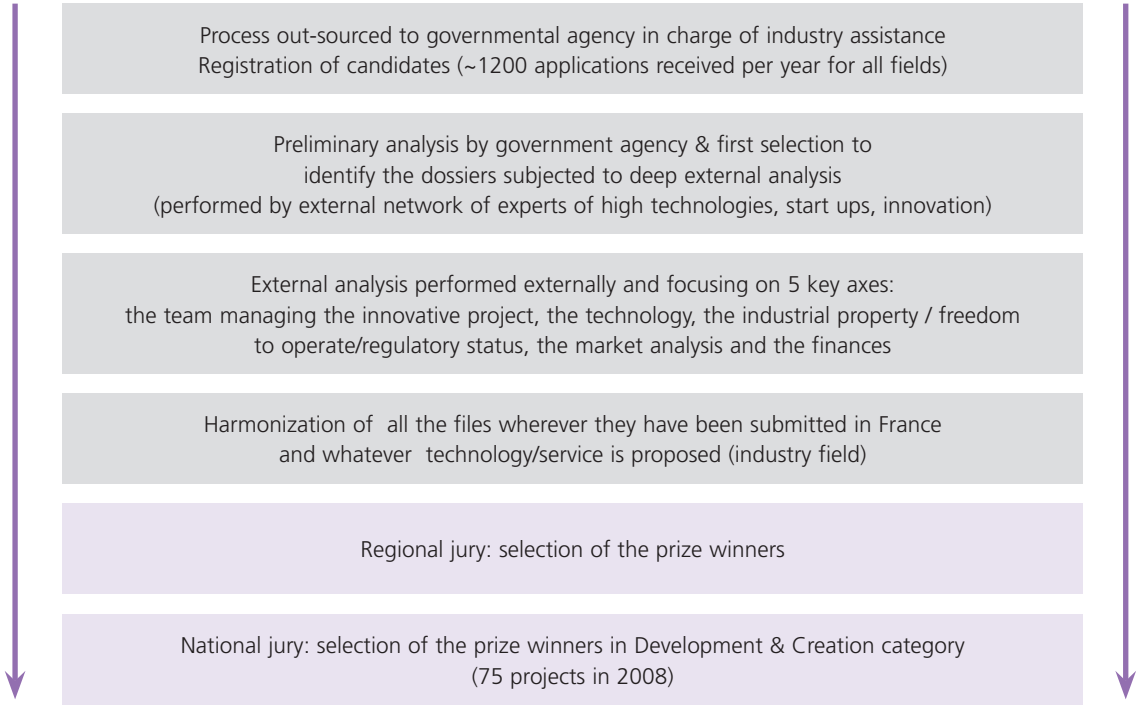
CNCETI case study: a National competition for the creation of innovating companies
This is an initiative of the French Ministry for Research, the 11th edition in 2009. The aim of this initiative is to stimulate the creation of innovating companies based on early technology developed mainly in the French academic institutions and universities, and to give incentives to people who create companies (financial incentives and recognition incentive (label)). Two categories are possible "Emergence" for a very early stage even at the concept level and "Development & Creation" for a project which already has preliminary elements of proof of concept:

- "Emergence" projects:
  Very early stage projects even at the concept level, not yet mature projects requiring the carrying out of preliminary feasibility studies (technical, economic, market, patentability) with allocated budget of maximum 45K€/project with an average incentive of 38K€/project.
- "Development & Creation" projects:
  Already elaborated projects upstream of company creation, with more complete Business Plan & Financial elements and particularly clear and secured industrial property and freedom to operate and allocated budget of maximum 450K€/project and an average incentive of 225K€/project.

All fields are concerned:



A complex process has been put in place to perform this national initiative to boost innovation at the national level:



This process takes into consideration all industry and technology fields as well as projects coming from all regions of the country leading to the necessity to combine proximity knowledge of projects (local economic development actors) and national harmonization view to allow the fairness between all fields and all areas.
In order to build sustainable and solid endogenous business fields, the identification of selection criteria that are transversal is considered as a key success factor. Five main criteria are used in this initiative as well as key sub-criteria depending on the category of the project. Ponderations between these criteria as well as the level of complexity associated with these criteria differ as well.

For instance, legal aspects that are treated at the level of „Emergence" are linked to patentability study prior to any filing, level of awareness of the project's team for industrial property and freedom to operate, level of formalization of contract collaboration between project's team and other stakeholders with a particular focus on the industrial property status. At the level of „development and creation", legal aspects are linked to the patent portfolio status, how strong are the patent applications, where they have been extended, what is the associated freedom to operate and what are the business and legal terms of the contracts with partners.

Selection and notation criteria:	
Human apsects: ■ Quality of businessman: determination, solidity, of leadership, curiosity, optimism, capacity of organization, capacity to make decisions, aptitude for the implementation ■ Competence to create company: experiment in project management, experiment of technology, capacity of communication, good distribution of roles ■ Knowledge and experiment of entrepreneurship: favorable personal environment, capacity to federate people, network	Technological: ■ Relevance of technology and competitive advantages : knowledge of the state of the art, degree of innovation, technological rupture, creation of value ■ Apprehension of the technical feasibility and value analysis: technological limits, R&D strategy, production of a prototype, remaining technical obstacles
	Market approach: ■ Market and applications segmentation, organization of the priorities for market access efforts ■ Competition analysis and importance of the competitive advantages ■ Determination of market access conditions and business model
Legal aspects: ■ Obligations towards current employers ■ Strategy of industrial protection: study of anteriority, patent filling, FTO, risks of counterfeiting ■ Clarity of the links with partners ■ Importance and knowledge of the legal environment	Financial: ■ Determination of a business model and of a coherent development plan ■ Determination of activity assumptions and financial simulations ■ Validity of financing assumptions for the beginning of activity

Such initiative allows in 12 years' time to identify and select more than 1000 projects in each category, leading to, for companies, the validation of the proof of concept (significant advance of the research and development program), the validation of the market demand and the economic reality of the project (economic feasibility study, market research), the reduction of cash burn rate, the recognized label "Oséo/Ministère de la Recherche" «concours national de création d'entreprise de technologies innovantes», the lever effect for banks and other financial partners; for the nation, the development of all technological fields

Emergence-Bio program from the National Research Agency (ANR) case study: a booster of emergence and valorisation of biotech projects having origin in academic laboratories
The creation of this program takes its source in the insufficient number of biotech technological innovations emerging from laboratories at the right level of development to be acquired by the industry.

Within the framework of Emergence-BIO, ANR wishes to support the complementary technological developments and studies, aiming to consolidate the proof of concept phase (*in vitro* and early *in vivo* data), the intellectual and industrial protection, and the potential exploitation of biotechnological inventions. This program is only dedicated to the academic research (not the industrial research). It has a strong link with the structures of valorisation of the organizations (university structures in particular). The call for tender is submitted to a strict two-steps selection process:

- A first selection performed by the office of technology transfer from the university or institution of origin leading the a selection yield of 10 to 50% depending of the selection pressure of the structure
- A second selection performed by a committee of people with scientific, clinical, marketing, patent or financing skills without any conflict of interest with the presented projects. The objective is that all the selected projects, at the conclusion of their financing, are the subject of a valorisation through the creation of a new endogenous company or a co-development with an industrial partners or a transfer of license to an industrial partner.

One of the major objectives of Emergence-Bio is to consolidate the Proof of Concept phase which is really critical for the economic return of the project and the sustainability of the system. In order to secure the quality of the work package within the proof of concept phase, the projects are split in thematic axes (AXE 1: Validation and optimization of new therapeutic products and new vaccines; AXE 2: Validation and optimization and/or pre-industrialization of tools and products for diagnosis in healthcare; AXE 3: Validation, optimization and/or pre-industrialization of technological tools and/or industrial bioprocesses for the production of bio-molecules and bio-drugs; AXE 4: Validation, optimization and/or pre-industrialization of technological tools for research in biotechnology; AXE 5: Validation, optimization and/or pre-industrialization of technological tools and/or industrial bioprocesses in the agricultural, agro-industrial and environmental sectors) and adequately distributed to the reviewers accordingly to their scientific and business skills.

Supporting Research and Development for the Field[68]
Diagnostic business field benefits from one of the strongest supports from an academic point of view, with more than 4 research centres involved, the Centre of Excellence for Translational Medicine, the Competence Centre for Cancer Research, the Centre of Excellence in Genomics, the Competence Center for Reproductive Medicine, as well as 3 major universities, the Tallinn University of Technology, the University of Tartu with the Institute of Molecular and Cell Biology and the Tartu University Hospital with its preclinical research centre and the Estonian University of Life Sciences.

The Centre of Excellence for Translational Medicine aims at taking a step towards multidisciplinary translational approach and linking two major research fields, neuroscience and immunology. Among all objectives of the centre, interviews underline the following: discovering clinical biomarkers through complex pharmacogenomic analysis, setting up an in vivo in animal bioimaging platform, develop projects in neurology and metabolic diseases (identification of new targets for psoriasis and type II diabetes, patient databases for Parkinson disease).
The Competence Center for Reproductive Medicine is one of the three new centres established in 2009, which focuses on human infertility diagnostics and treatment, as well as human and animal assisted reproduction. The focuses of the Centre's research are novel approaches for human infertility diagnostics, advances for human and animal assisted reproductive technologies (ART), microecological approaches for human reproductive biomedicine. The research directions include foetal genetic testing chips, endometriosis diagnostics and metagenomics applied to reproductive medicine.

The diagnostic business field is the field that benefits the most from the support from other very strong disciplines in Estonia, such as bioinformatics (e.g. data management), genetics or biosensors' technology, being at the centre of several scientific subjects. This leads to a strong critical mass of scientific complementary workforce dedicated to diagnostic challenges.

68 Interviews with Estonian stakeholders

This critical mass of academic research is also reinforced by strong Estonian key opinion leaders at international levels.

Education

- In order to get the right level of scientific excellence to bear the international competition as well as a locally based workforce, additional training could be set up, such as autoimmune disorders specialization, formulation and drug development topics, manufacturing development subjects (upstream, downstream, analytical development)
- In addition to that a large gap still remains for industrial property skills, business development good practices and biotech business management experiences.

Summary

A potent short to mid-term opportunity with long-term possibilities for Estonia:

Strengths	**Weaknesses**
■ A strong critical mass in health diagnostic, both endogenous and exogenous, to rely on for in-licensing opportunities and research and internal development. ■ A critical mass in the academic research and development with more than 4 centres of excellence and 3 universities. ■ Emerging portfolio of patent applications. ■ Highly qualified research and development workforce (publications in peer review journals). ■ A couple of internationally recognized Key Opinion Leaders. ■ A critical mass of project submitted for grants and funding.	■ Limited number of patent filed. ■ Lack of industrial property skills (patent filing, prosecution, litigation) to further support academic researchers ■ Limited number of PhD. ■ Lack of dedicated health-specialized VC (with good understanding of correlated timelines and ROI). ■ Lack of investment. ■ Lack of structuring equipment (in vivo in animal bioimaging equipment). ■ Lack of specialized business development skills for transfer of projects from university to the industry.
Opportunities	**Threats**
■ An opportunity for the Estonian biotech companies, mainly focused on services, to slightly move to a more balanced model of services (short-term objectives) and biomarkers product development, to increase the value of the company and build long-term business field. ■ Therapeutic areas and indications (oncology, CNS, autoimmune diseases) where there is still a lack of diagnostic, prognostic and stratification biomarkers. ■ A niche opportunity around reproductive medicine to explore further under a loco-regional market (Estonia, Baltic countries, proximal Russia) and to develop in close relationship with therapeutic development business field. ■ The need for a strong political support for the in vivo in animal imaging centre to help becoming the National centre (for both diagnostic and therapeutic objectives) and a model for academia and industry as well as for Baltic and Scandinavia. ■ The strong growth of patient population suffering from CNS disorders due to an aging population, e.g. Alzheimer's and Parkinson's disease, leading to one of the main health care issues by 2050. ■ The existence of public-private partnerships for biomarker research and development, such as the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium and the Alzheimer's Disease Neuroimaging Initiative (ADNI). ■ A progressive shift in the healthcare system towards proactive testing rather than reactive testing, expected to drive growth in IVDs. ■ Increased information in genomic, proteomic and metabolomic databases to improve identification of biomarkers through the human genome project and International HapMap project.	■ An on-going and stronger competitions on oncology biomarkers. ■ An emerging competition on CNS biomarkers. ■ The level of investment necessary to develop clinically validated biomarkers. ■ The strong National support needed to further develop such areas.

Conclusion about the Potential for Estonia

- A potent short to mid-term opportunity with long-term possibilities for Estonia with close links with therapeutic development and drug discovery business fields
- A clear area to invest, both from an early stage, with a point of view to enable technologies that support biomarker discovery, such as, bioimaging tools, bioinformatic (to be closely correlated with drug discovery field) and from a biomarker development and validation point of view.

1.6.3 Drug Discovery Technologies[69]

Introduction

Definition of the Field

In the fields of medicine, biotechnology and pharmacology, drug discovery is the process by which drugs are discovered and/or designed.

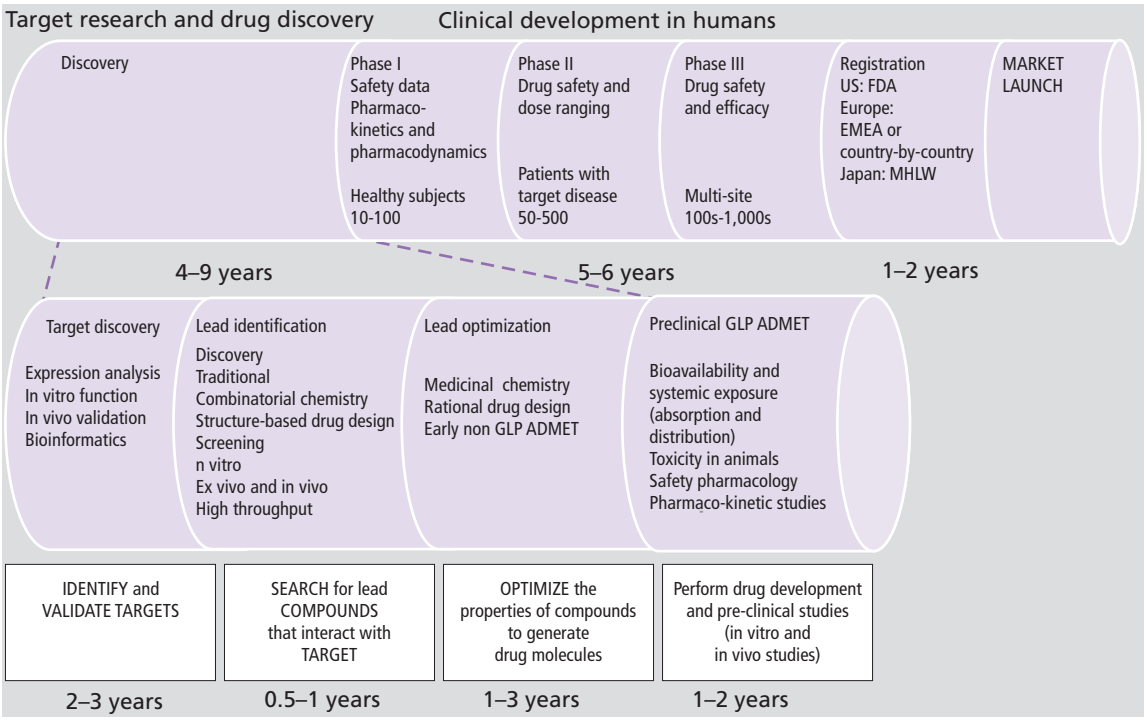


Figure 15: Drug development phases[70]

Recent analyses indicate that despite a more than double increase in the pharmaceutical research and development budgets in the past decade, the number of drugs approved by the FDA has dropped from 24 in 1998 to 13 in 2006. Pharmaceutical and biotechnology companies are under immense pressure to produce a steady stream of innovative, well-differentiated drugs at reduced costs. Currently, it takes an estimated fifteen years and US$1.7 billion to develop and launch a drug in the market, with US$800 million spent on taking a drug through research and development. As a result of the rising costs, innovators often concentrate their efforts on products with potentially high market return.

The discovery phase includes target discovery, hit and lead identification, lead optimization and preclinical non-regulatory (so-called early) ADMET. Certain discovery phases can support both drug development but also biomarkers identification and validation with certain specificities obviously. Drug discovery process suffers from a huge attrition rate including 3 logs for the discovery steps only.

69 *Overview of the European Drug Discovery Market*, Frost & Sullivan, 12/2008
70 Ernst & Young knowledge

The process of drug discovery has indeed limitations, such as the need to analyze drug candidates in a more rapid and accurate manner. Hence, there seems to be an emerging opportunity to develop new tools that may aid in the drug discovery process. The pharmaceuticals industry has invested heavily in technologies, such as automation (HTS/HCS) and liquid handling systems and lab-on-a-chip or microfluidics technologies that increase throughput, decrease costs and provide access to new classes of scientific data. Currently, nanotechnology promises to exponentially increase even the volume of microarrays by working at a level far smaller than conventional microarrays.

The discovery phases strongly rely on these very different and potent technologies, currently emerging, such as high-content screening, nanotechnology, bioinformatics, microfluidic, microarray, lab-on-chips or biosensors and other so-called enabling technologies. These enabling technologies may not be processed independently due to the interdependency of one from another: for instance a lab-on-chip for a diagnostic kit is based on a biosensor systems requiring nanochip or equivalent coupled to a signature of biomarkers identified through HCS and which may generate a large amount of biodata that need bioinformatics tools to be processed properly.

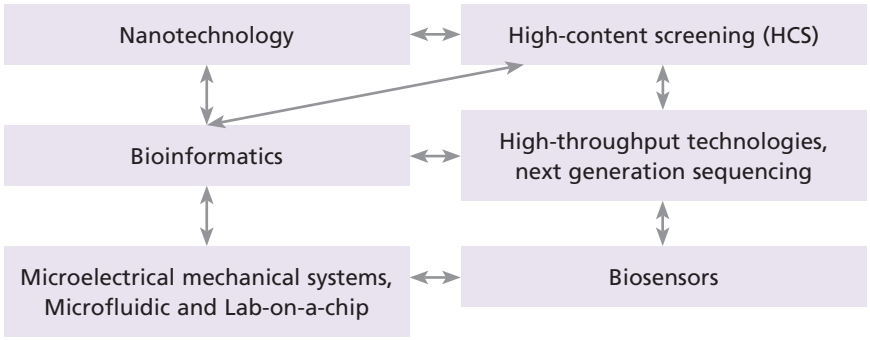


Figure 16: Drug discovery interdependent tools[71]

Examples of Products and Services
Among the most promising discovery enabling technologies that are emerging, RNAi, Lab-on-Chips, Bioinformatics tools and High-content screening (HCS) are subjected to deep analysis.

RNAi definition:
RNA interference (RNAi) is the process whereby normal cells utilize pieces of short double-stranded RNA (dsRNA) to prevent expression of specific genes by disrupting the process of mRNA translation to proteins.

RNAi can be of different types:
- si RNA: Short interfering RNAs (siRNAs) made of duplex RNA molecules of typically 20-25 nucleotides
- dd RNAi: DNA-directed RNA interference (ddRNAi)
- Micro RNAs (miRNAs): small single-stranded RNA molecules, typically 21-23 nucleotides
- Short Hairpin RNAs: single-strand RNAs containing a high degree of secondary structure.

Lab-on-Chips definition:
LOC is a term widely used for any kind of research with the goal of miniaturizing chemical and biological processes. It is not a well-defined scientific term. LOC technologies include micro-fluidic chips as well as non-fluidic miniaturized systems, such as sensors and arrays (the so-called biochips).

Bioinformatics' tools definition:
Bioinformatics is the science that deals with the collection, storage and analysis of genetic and protein-related data that can be applied to gene-based drug discovery and the development of biotechnology. The potential of bioinformatics is nothing less than the rational, targeted design of drugs.

71 *Overview of the European Drug Discovery Market*, Frost & Sullivan 12/2008

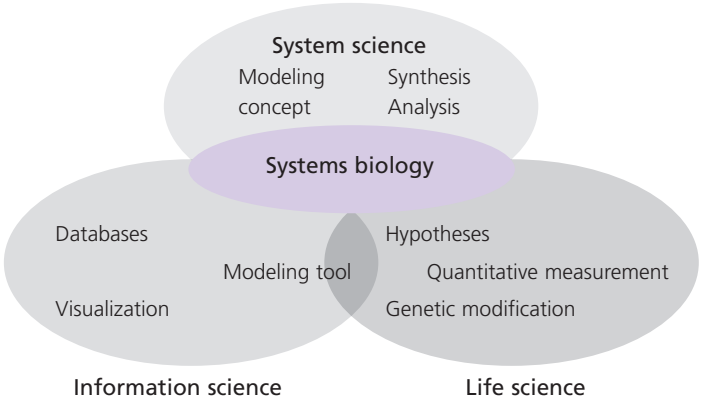


Figure 17: „Modeling" diseases on the molecular/cellular level[72]

The -omics revolution – systematic genomic, proteomic, and metabolomic has led to the development models of the complex biological systems and diseases, collectively called the systems biology.

One perspective of the systems biology is application of data analysis, mathematical modelling and computational simulation methods to study the function of biological systems.

The systems biology is about coordinating the study of biological systems, by investigating the components of cellular networks and their interactions, applying experimental high-throughput and whole-genome techniques and integrating computational methods with experimental efforts.

HCS definition:

- High-Content Screening (HCS) can be defined as an automated multiplex imaging approach to understanding complex activities in cellular assays for measurement of spatial distribution of targets in cells, individual and organelle morphology, and complex phenotypes.
- HCS covers large numbers of parameters in parallel, massive data sets that require immense storage capacity and IT capabilities, especially in drug discovery and systems biology.
- HCS has made possible the analysis of multiple events within a cell at a single time.
- Better image analysis and image file management will be essential: data mining of existing databases, refinement of image processing, data analysis needed for multi-parameter data sets
- Software solutions are expected to play a major role, and in particular, software solutions supporting the extraordinary requirements of cellular HCS (ultrahigh-speed, cutting edge and reliable image analysis, vast data amount).
- Oncology is found to be the main research area for HCS.

International Business Potential

International Market Size and Growth

In 2007, the Western European drug discovery market was worth US$17.40 billion in revenues. By 2014, the revenues are expected to reach US$42.08 billion, with a compound annual growth rate (CAGR2007-2014) of 13.5%.

72 *Biology in Practice*, Klipp, E Wiley-VCH Systems, 09/2007; *Opportunities for Bioinformatics in the EU*, Frost & Sullivan 2007; Ernst & Young; *Emerging technologies in systems biology*, Frost & Sullivan, 06/2008

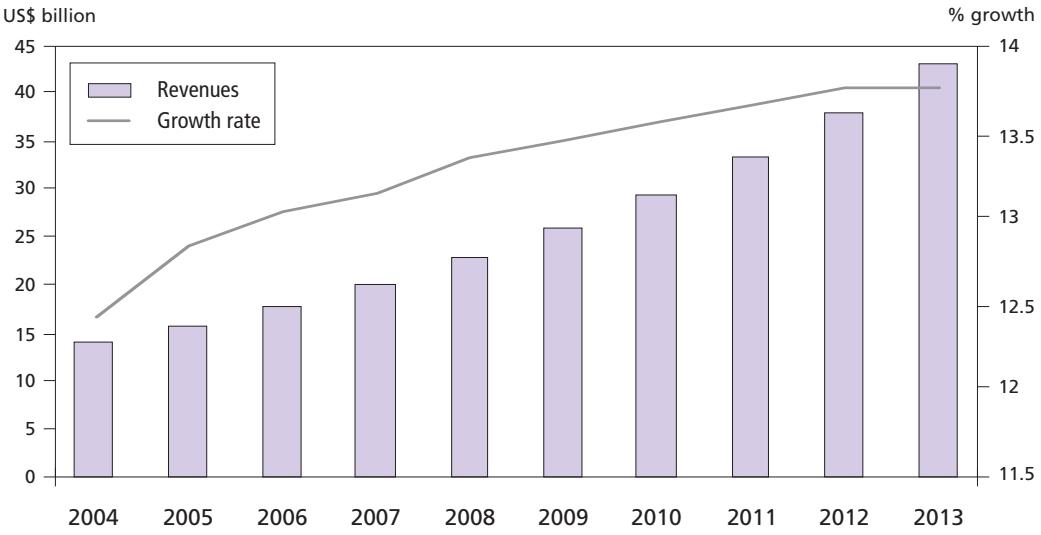


Figure 18: Revenue growth in the Western European drug discovery market 2004–2013[73]

This is largely due to the advancements in technologies, such as RNAi, gene expression and the development of live cell assays, laboratory automation systems and other research tools.

In 2008, revenues in the total RNAi market amounted to approximately US$133 million. The CAGR for 2005 to 2012 is estimated at 23.8%. Revenues were generated by the sales of RNAi content, RNAi delivery tools, and RNAi screening and analysis tools. Revenues from these three market segments totalled approximately US$52 million, US$10 million, and US$38 million respectively.[74]

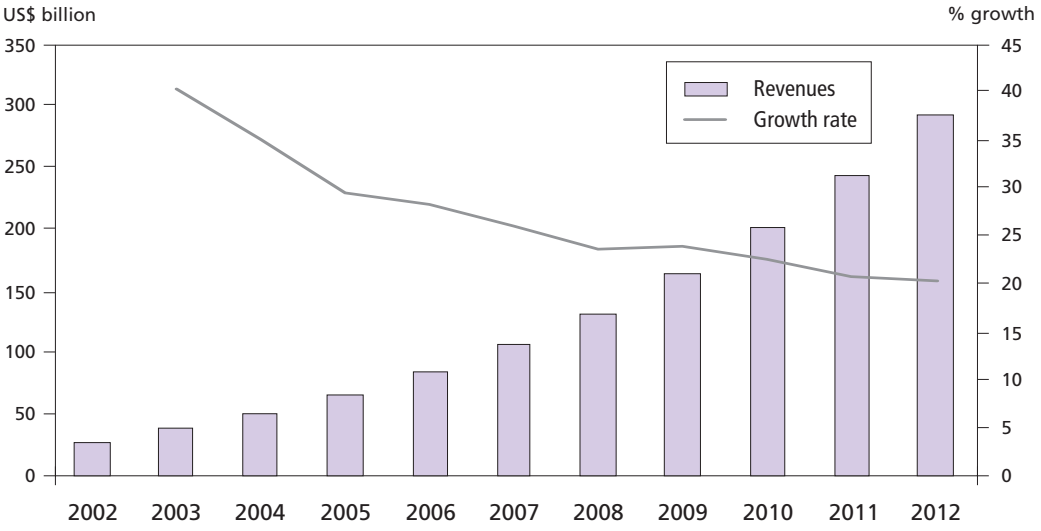


Figure 19: Total RNAi Market: Revenue Forecasts in USD mio (U.S.), 2002–2012

Revenue forecasts (Europe) for Lab-on-chip and microfluidics market, 2005-2015, are expected to reach US$1,083 million by 2012. The revenues are likely to reach US$1,615.2 million in 2015, growing at a compound annual growth rate (CAGR) of 13.5% from 2008 to 2015. Competition is increasing but still remains manageable.

73 *Overview of the European Drug Discovery Market*, Frost & Sullivan, 12/2008
74 *World RNAi Markets*, Frost & Sullivan, 07/2004; *World RNAi Markets*, Frost & Sullivan, 05/2006

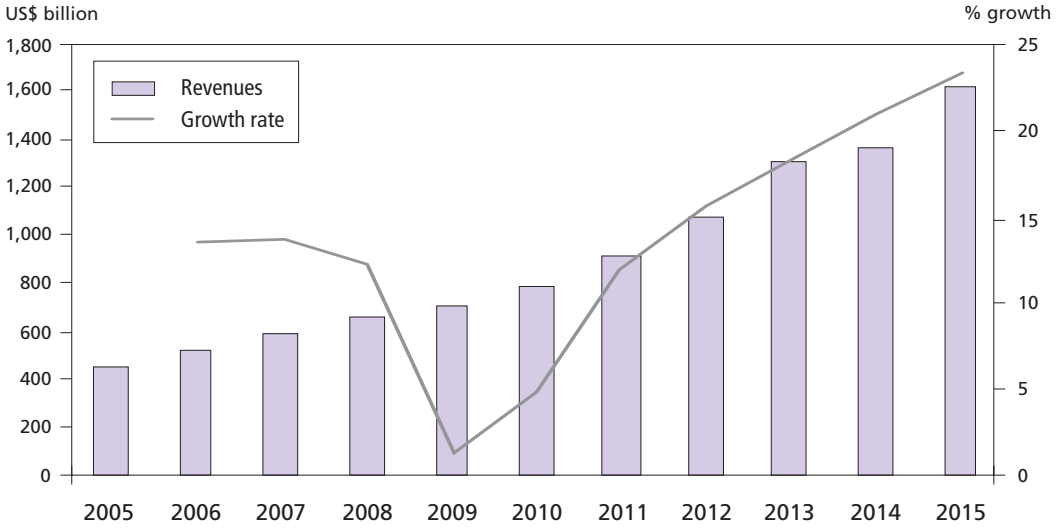


Figure 20: Total Lab-on-chip and Microfluidics Market: Revenue Forecasts (Europe), 2005–2015
Source: Frost & Sullivan, European Lab-on-chip and Microfluidics Markets (05/2009).

The highly fragmented nature exhibited by the European Bioinformatics discovery market has made calculation of market revenues extremely difficult. The total European Bioinformatics market is expected to be worth US$ 392 million in 2006 with a growth rate of 11.8%. The market shows an increase in growth rate compared to 10% in 2004.

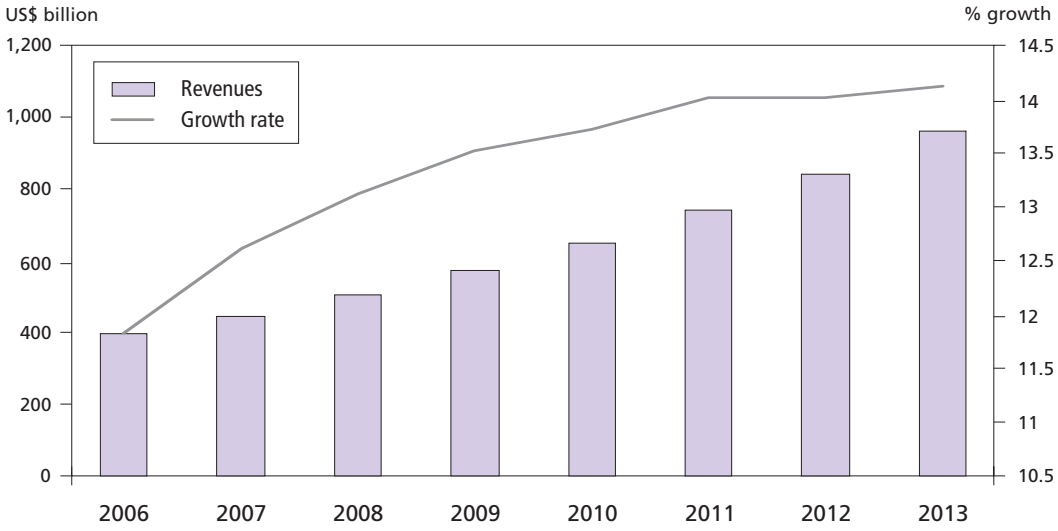


Figure 21: Opportunities for Bioinformatics in Drug Discovery Market: Revenue Forecasts in USD Million (Europe), 2006–2013
Source: Frost & Sullivan, "Opportunities for Bioinformatics in the EU", (2007)

In 2007, the screening market which includes the HCS market was worth US$10.01 billion in revenues. The market is expected to grow with a CAGR of 14.4% from 2007 to 2014, to reach revenues of US$ 25.65 billion by 2014. The degree of competition is high and the field is already saturated.

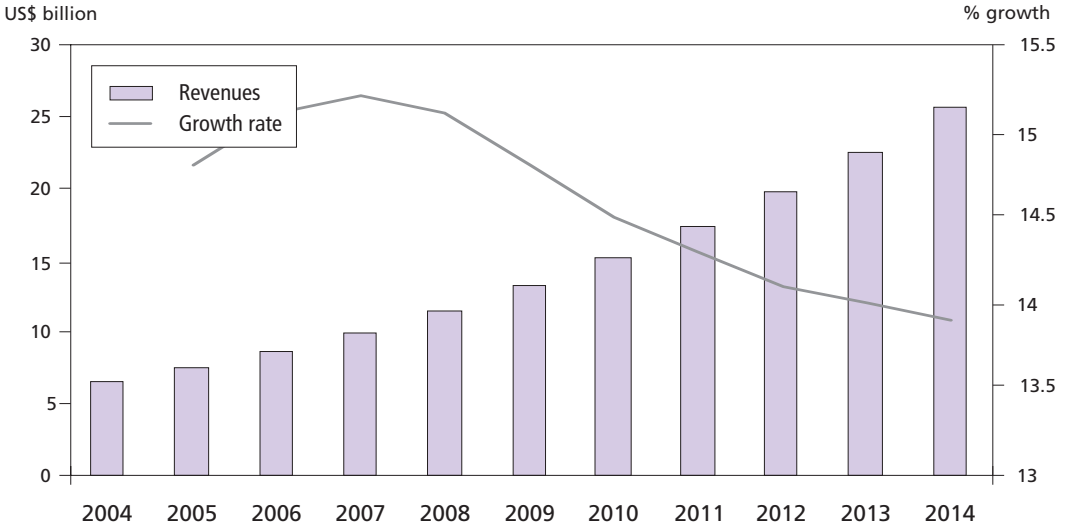


Figure 22: The screening market including HCS market [75]

Trends and Developments

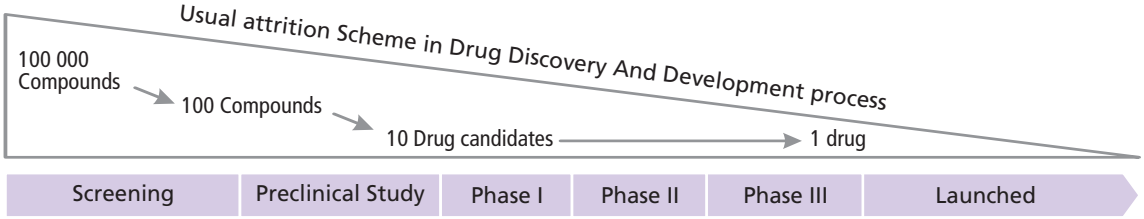


Figure 23: Attrition scheme in drug discovery and development process

The future trend in drug discovery lies in the growing interest in biomarkers. The development of technology platforms for measuring the biomarkers that are indicators of disease stages or compound toxicity is a promising avenue for streamlining the entire drug discovery process. In addition, fragment-based drug discovery and fragment based screening, together with label-free technology, high content screening (HCS) and predictive drug discovery with the use of silico platforms is likely to drive the drug discovery market.

The whole challenge is about screening more compounds in less time and at lower costs

- The field of drug discovery has been a slowly progressing, as only a handful of several thousands of compounds discovered enter and actually pass the clinical trials. This makes the process of discovering and developing new drugs a time-consuming and multibillion dollar business. Here is where concepts, such as microfluidics and LOC technologies are believed to contribute by way of aiding the potential synthesis of thousands of individual molecules in microchannels in minutes, instead of the hours and days needed using traditional drug discovery methods.
- All of these have led to a shift of technology from traditional time consuming methods toward combinatorial and high-throughput chemistry – which produce a wide range of chemically diverse sets of compounds for the lead discovery process. Automation and miniaturization are the key concepts that have helped accomplish these developments. Researchers expect the use of these enabling technologies for a more efficient identification of lead compounds and a quicker screening of a large number of compounds in smaller quantities.
- The future of medicine and drug discovery is likely to act as a preventive measure against disease on an individual basis. However, this will require a thorough understanding of the pathological processes underlying the human biological system using certain enabling technologies. This will lead, in the more immediate future, to the development of simple diagnostic devices, which will be used to identify common diseases through either invasive or non-invasive techniques. As diagnostic devices become more complicated and the knowledge base increases, the market will be driven by a need to move away from reactive medicine and toward preventive/predictive maintenance.

75 *High Content Screening for Target Identification and Validation*, Frost & Sullivan, 06/2006, High Content Screening: Science, Techniques and Applications, Haney, Steven A 2008

Time to Market

Enabling technologies for particular applications are relatively short to mid-term projects, as they often give the opportunity to propose services while developing such technological tools products. Average estimated timelines to develop such a product are in the range of 2 to 4 years whoever allowing simultaneous commercialization of services to research purposes.

Important International Market Participants

Example of companies dedicated to discovery phase of development includes:

- Caliper Life Sciences is a leading solution provider for drug discovery and life sciences research for the pharmaceuticals and biotechnology industries. Caliper presently has two microfluidics-based instruments, and a variety of consumable chips. The LC3000 LabChip3000 performs enzymatic and cell-based assays and the LC90 LabChip 90 is used for DNA and protein separations.
- Accelr8, a Denver-based biotechnology company, develops a new LOC that can identify single bacterial cells for the most common cases of drug-resistant pneumonia, cutting down the wait from days to hours. The technology could also help in the development of new drugs.
- Biowarn LLC, a Montgomery Village, MD-based biotechnology research and product development company, deals with sensor technology, SmartSense, to create a biochip that can detect the deadly avian flu virus (the H5N1 strain). In addition, this sensor can be potentially applied for the detection of the human immunodeficiency virus (HIV); tuberculosis; hospital-acquired infectious agents, such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), or Escherichia coli (E. coli); bio-terror agents, such as, anthrax or smallpox; or any biomolecule that can bind to a SmartSense detector.
- Bioscora, a young German biotechnology company, has come up with the first of its kind of LOC called protein MAP.screen for multiplexed analysis of kinase signalling pathways which the company has launched recently. The protein microarray contains 14 arrays per slide. They contain 10 antibodies for the very rapid multiplexed profiling of 3 MAP kinase signalling cascades. This aid in monitoring the activation and thereby determining the role of important biological pathways. The product is based on the principle of a label-free on-chip detection platform. The company is commercializing this breakthrough by licensing it through another company that it has licensed its technology to, called IQ Micro.
- Cellix Limited, an Ireland-based instrumentation company's has developed the Microfluidic SP1.0, which models human blood vessels, providing scientists with a dynamic set-up mimicking physiological conditions to test new therapeutic drugs.

At international level, Europe is more focused on enabling technologies compared to North America because discovery tools companies may be more services-oriented in terms of the business model and then it is easier to set up without huge financial investments as it is the case in therapeutic or even diagnostic development. This is confirmed by the European industry segment analysis published in Beyond Borders Global Biotech Report 2006 (Ernst & Young internal publication), which has shown that privately held companies are much more involved in discovery services and –omics enabling technologies of public company profile that are closer to the industry segmentation in the North America.

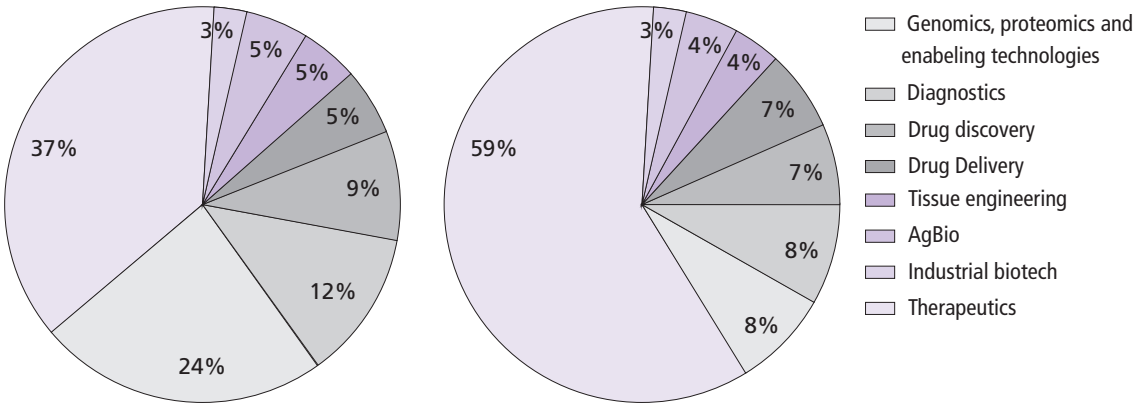


Figure 24: European industry segment (Beyond Borders Global Biotech Report 2006)

Identified Bottlenecks
A couple of challenges in discovery process remain unsolved, such as:
- the difficulty to expand bioinformatics tools to non-specialized end-users, currently one of the major challenges faced by the European bioinformatics industry and expected to continue having a high impact in the future,
- the necessity to continuously adapt bioinformatics tools to the rapid changes in the IT field
- the lack of standards in bioinformatics requiring better integrated systems, algorithms, annotation protocols and user interface development,
- the limited integration of data from different sources in bioinformatics,
- the necessary accuracy, reliability and consistency of sensitive bioinformatics data with regulatory compliance issues (patents or copyright protection),
- some specific technological challenges of microfluidic and LOC technologies (signal to noise ratios),
- the correlated achievement of integration in these assembling and interfacing individual components to achieve total integration in working systems,
- costs related adequacy with the use of the technology

Assessment of Estonian Potential

Existing Production and Companies with the Potential for Future Implementation
The Estonian health industry is mainly involved in discovery processes, with mostly small endogenous companies as described in sections diagnostic and therapeutic business fields. This business field has been the early developed in Estonia due to its proximity to research phases as well as its relative easiness to run simultaneously services activities for short-term turnover purposes as well as longer-term and higher value technology development.

Existing or under development products / services
- RNAi silencing suppressor technology
- Peptide libraries
- Innovative microarray technology
- Estonian Genome project / Evolutionary genetics

Examples of companies involved in the discovery business field
Estonian endogenous companies include Celecure AS, ProtoBios AS, InBio OÜ, Bestenbalt LLC., Kinasera, LabAs Ltd., Asper Biotech AS, Docobo Ltd, FibroTX Ltd., Immunotron, Medisoft, OÜ TorroSen, EGeen AS – Quertec.

Exogenous companies involved in discovery steps include Applied Phenomics LLC, IasGen Ltd., Molcode Ltd, Biotap AS, Evotec.

This discovery business field is the most suitable for service models allowing at the same time the development of longer-term products. However, interviews pointed out the same limit identified in the other health business fields: a lack of patent filing habit, a limited number of patents filed, limited amount of extensive business deals, a lack of business/corporate development skills.

However at least 2 patents have been filed in this field:
- a patent application filed by Baltic Technology Development Ltd. (sister company of MolCode Ltd.) about "Oligonucleotides with modified bases in hybridization of nucleic acids, polymerase chain reaction and siRNA-mediated gene silencing"
- and a new patent application related to the RNAi silencing technology.

International collaborations occurred in this field with ProtoBioS in October 2005, which entered into a contract with the enterprise OncoTx (California, USA) for conducting research on the regulation of the isoforms of the co-regulators of transcription in melanomas. This type of international business collaboration should be strongly and further supported.

Supporting Research and Development for the Field
The Discovery business field is the field which is the closest to the research in terms of positioning on the value chain, the nature of the required workforce, the type of work performed.

This field strongly benefits from the strengths of Estonia at research level with bioinformatics, genetic and genetic tools, physics.

Most of the Estonian research is involved in the discovery field with at least 2 competence centres (Competence Centre for Cancer Research, Competence Centre for Reproductive Medicine and Biology), 3 centres of excellence (Centre of Excellence in Genomics, Centre for Integrated Electronic Systems and Biomedical Engineering, Centre of Excellence in Chemical Biology) as well as universities (Tallinn University of Technology with the Centre for Biology of Integrated Systems, the Institute for Genomics and Proteomics, Institute for Molecular Technology, Institute for Gene Technology, Institute of Chemistry, Department of Electronics (Centre for Biorobotics) and University of Tartu with the Institute of Molecular and Cell Biology) and institutions (National Institute of Chemical Physics and Biophysics (KBFI) and Estonian Biocentre).

This very strong critical mass of academic research is supported by substantial Estonian key opinion leaders at international levels publishing in recognized journals worldwide (see the research and development section of this report).

A couple of projects are on-going in this field:

- Development of an innovative technology using RNAi silencing suppressors to modulate cancer-specific miRNA levels
- Intelligent design of peptide libraries and technology for anti-cancer biomarker discovery
- Innovative microarray technology

Summary

A potent short- to mid-term research and development opportunity for Estonia:

Strengths	**Weaknesses**
■ A critical mass in the discovery field, both endogenous and exogenous with short-term activities and long-term product development. ■ The largest critical mass in academic research and development with 2 competence centres, 3 centres of excellence and a couple of universities with specialized departments and institutions. ■ Early stage portfolio of patent applications. ■ On-going international business collaboration. ■ Highly qualified research and development workforce (publications in peer review journals). ■ A couple of internationally recognized Key Opinion Leaders. ■ A critical mass of project submitted for grants and funding.	■ Limited number of patent filed. ■ Lack of industrial property skills (patent filing, prosecution, litigation) to further support academic researchers. ■ Lack of dedicated specialized seed funding (with good understanding of correlated timelines and ROI). ■ Lack of process for project selection in particular in the case of highly competitive fields (RNAi). ■ Lack of specialized TTO used to support project maturation.
Opportunities	**Threats**
■ A shift of strategy in pharma and biotech companies to collaborate including at the discovery stage due an increasing lack of internal innovation capacity. ■ An evolution of the structure of the industry research and development towards a network of centres of excellence at international level giving a great opportunity for Estonia to play a role at international level as one particular centre of excellence. ■ An increasing need of complementary technologies to allow innovation (sensors and microarray or LOC). ■ A couple of bottlenecks in bioinformatic or biology integrated systems requiring exactly the core strengths existing in Estonia.	■ Industrial patent policy, new research and development projects, new endogenous company, and innovation need to be supported (financially) much more in Estonia to compete at international level. ■ The size of the business associated with discovery remain lower than therapeutic, diagnostic or food industry business and is still mainly made of smaller companies limiting obviously the potential size of the whole field.

Conclusion about the Potential for Estonia

The discovery business field is one of the strongest biotech business fields in Estonia with one marketed product as well as a couple of launch and working services. One large international company operating in the field, Evotec (Germany, UK, Estonia), is implanted in Estonia as well. This field is strongly supported by bioinformatics Estonia workforce, leading to a real critical mass. Bioinformatics area is also an opportunity for short- to mid-term opportunity for both services and products and is clearly an area where there are still huge unmet needs (data management, integration, standardization). RNAi projects may suffer from the current aggressive competition on this subject and are consequently compelled to file robust and critical mass of patent applications in order to survive.

This field is the best sector for mix models of both service and products run simultaneously.

This is clearly an area to support for both short- and long-term perspectives.

Opportunities:
Emerging opportunity to develop new tools supporting drug discovery process: RNAi, gene expression and the development of live cell assays, laboratory automation systems and other research tools. Live cell assays based on High-Content-Screening (HCS), the newest most important sectors in pharmaceuticals research and development, is driving a wave of new opportunities for investment on both the supply and demand sides, as new hardware systems, software applications and reagent kits are enabling researchers to study intracellular events on cells.

1.6.4 Bioprocessing

Introduction[76]

Definition of the Field

A bioprocess is any process that uses complete living cells or their components (e.g., bacteria, enzymes, chloroplasts) to obtain desired products. In the healthcare sector, bioprocessing covers the production of different types of biologics:

Biologics not derived from recombinant DNA:
- biologic extracts (hormones, enzymes, polyclonal antibodies, plasmatic proteins)
- traditional vaccines
- cell and tissue therapy products.
- Among the biologics not derived from recombinant DNA, only cell and tissue therapy products are considered as in the enlarged scope of biotechnology.

Biologics derived from recombinant DNA:
- nucleic acids (oligonucleotides and plasmids, DNA vaccines, gene therapy)
- recombinant proteins (therapeutic proteins, monoclonal antibodies, recombinant and therapeutic vaccines)

Stem cells

Stem cells are an emerging market, with limited current applications in replacement for bone harvesting in spine fusion surgery, bone growth and void fill in fresh fractures, and bone growth and void fill in non-union fractures. However, stem cells are likely to represent a disruptive new treatment class, with radical changes in the treatment of total knee implants, sports medicine, heart muscle repair following heart attacks, improvement of heart irrigation through stimulation of angiogenesis, bone marrow transplants and inflammation. The US stem cell market was estimated to be worth US$37 million in 2007 and US$2 billion in 2012. Europe has been much more suspicious on stem cell therapies resulting in an important domination of the market by the US. Asia is considered as up-and-coming, especially China. Overall, more than 200 companies are developing stem cell products worldwide.

76 *Bioproduction 2008, Etat des lieux et recommandations pour l'attractivité de la France*, Leem Biotech & Genopole, Developpement et Conseil, Octobre 2008; Nature Biotechnology in *Bioproduction 2008, Etat des lieux et recommandations pour l'attractivité de la France*, Leem Biotech & Genopole, Developpement et Conseil, Octobre 2008; IMS Health in Bioproduction 2008, *Etat des lieux et recommandations pour l'attractivité de la France*, Leem Biotech & Genopole, Developpement et Conseil, Octobre 2008; *Stem Cell Market Analysis Fact Sheet*, 5th annual Stem Cell Summit website, http://www.stemcellsummit.com; *Bit player or powerhouse? China and stem-cell research*. Murray F, Spar D. N Engl J Med 2006;355:1191–4; EY internal experts

Nucleic acids

Nucleic acids form an emerging sector with only 2 products on the market (Vitravene, Isis Pharmaceuticals/ Novartis and Macugen, Eyetech/Pfizer) for a market size of US$30 million in 2007.

Regarding gene therapy in particular, only one product is commercialized today: Gencidine (authorized in China in 2004, Shenzhen SiBionon). About 200 clinical studies on gene therapies are currently ongoing in Europe, mostly for cancer (66%) and cardio-vascular (10%), infectious (8%), and monogenetic pathologies (8%) indications. The global market for gene therapy treatments is predicted to be worth US$5.3 billion in 2011. Gene therapy can be conducted *in vivo* (direct injection of prepared transgene) or *ex vivo* (in vitro transfection of the transgene in cells taken from the patient and then reinjected). In both these cases, the transgene must be carried by a vector and its choice is a key issue today. Vectors used are of two types: viral (e.g. adenovirus, herpes simplex virus, lentivirus) or non viral (e.g. liposomes, electroporation, plasmids).

Recombinant proteins

The recombinant proteins market is the most mature biologics market, representing almost all of the total biologics revenues. The first recombinant biologic put on the market was recombinant insulin by Eli Lilly in 1982 in the US. Therapeutic proteins (growth factors, hormones, cytokines, fusion proteins, plasmatic factors and enzymes) represent more than 2/3 of the market, whilst monoclonal antibodies represent little less than 1/3 and recombinant vaccines 1,5%. Recombinant proteins can be produced in isolated mammalian cells (e.g. CHO) or microorganisms (e.g. yeast).

Novel approaches have also included producing biologics in transgenic plants or animals. In fact, the field of human medicine represents the greatest part of transgenic animal research for commercial use, with therapeutic proteins being produced in the milk, blood, or eggs of genetically engineered animals. The first such a drug to be approved by the European Commission was an anti-coagulation drug derived from the milk of genetically engineered goats in 2006.

Other than a differentiation by types of biologics produced, bioprocessing can be separated according to the different end-uses:

- production for preclinical research (very limited quantities, limited regulatory and quality requirements – optimally regulatory preclinical is also done in GMP (good manufacturing practices)). Non-GMP production is usually done in small research and development laboratories, representing a highly fragmented and limited market. It is not studied here.
- production for clinical trials (limited amounts especially for early clinical phases, GMP required)
- commercial production (large amounts, GMP required).

Examples of Products and Services

Recombinant proteins

In 2007, 24 biologics obtained the status of blockbusters, meaning they generated revenues of more than US$1 billion. All of them are recombinant proteins (among which 7 monoclonal antibodies (e.g. Remicade, Herceptin), 6 growth factors (Aranesp, Neulasta), 4 hormones (Lantus, Humalog) and 4 interferons (Avonex, Pegasys)). The biologics market leader is Etanercept marketed under the trade name Enbrel, with US$5.3 billion revenue in 2007. This fusion protein is a TNF inhibitor indicated for the treatment of autoimmune diseases. It was created in the early 1990s by researchers of the University Of Texas Southwestern Medical Center at Dallas and developed by Immunex, a biotechnology company that was then acquired by Amgen in 2002. Enbrel is co-marketed by Amgen and Wyeth in North America, and by Takeda Pharmaceuticals in Japan. In the rest of the world it is marketed by Wyeth (recently acquired by Pfizer).

Production of recombinant proteins in transgenic animals

- GTC Biotherapeutics (US) developed an Antithrombin III, ATryn derived from the milk of transgenic goats. This protein was approved in 2006 by the European Commission for the treatment of hereditary antithrombin deficiency. The FDA approved the drug in February 2009;
- Research on chicken eggs as bioreactors for the production of human therapeutic proteins is ongoing at the Roslin Institute, Edinburgh.

Stem cells

- Products expected to be approved by the FDA in the coming 3 years are:
- Prochymal (Osiris Therapeutics, Inc, US): treatment for acute graft versus host disease (GvHD), an immune condition that can affect cancer patients who have received a bone marrow transplant. Two separate multi-center Phase III human clinical trials are currently being conducted.
- Chondrogen (Osiris Therapeutics, Inc, US): regeneration of the meniscus in the knee, and prevention of osteoarthritis. A Phase I/II clinical trial is ongoing.
- 2 or 3 treatments for damaged heart muscle due to heart disease.

International Business Potential[77]

International Market Size and Growth

Biologics represented a global market of US$71 billion in 2007 (10% of the global pharmaceutical market) and this market grew by 17% in 2007 (whilst the global pharmaceutical market grew only by 7.2%). The main reason for this is that biologics represent a growing part of therapeutic innovation: 30% of the molecules that came to market in the last 4 years were biologics.

Recombinant proteins

Recombinant proteins represented more than 99% of the global US$71 billion biologics market in 2007.

In terms of production, the total global capacity for recombinant proteins is estimated to be around 3 million litres in 2008 (excluding vaccines and biosimilars). 30% of this capacity belongs to CMOs. There are more companies doing bioproduction of recombinant proteins and vaccines in Europe (69) than in America (57) and Asia & Oceania (10). The same distribution is observed considering the number of production sites (respectively: 123, 97 and 22). This is due to the greater presence of clinical lot producing CMOs in Europe.

In Europe, the leading countries are Germany (25 production sites), UK and France (both 16 production sites). However, concerning commercial lot production, Ireland and Switzerland concentrate an important number of bioproduction facilities.

In the Baltics, 11 bioproduction sites have been identified in 2008:

- 8 commercial lot sites: 2 in Stockholm region, one in Vilnius and 5 in Medicon Valley,
- 4 clinical lot sites: 2 in Finland and 2 in Sweden (all of these belong to CMOs).

The global bioproduction capacity has grown by 30% since 2005, mainly due to the opening of new facilities by large biotech and pharmaceutical players (e.g. Genentech, Amgen, and Novartis). Capacities of microbiology based bioproduction should stabilize from 2009 around 1 million litres, while capacities of mammalian cell-based bioproduction should continue increasing by 15% a year from 2 million litres in 2008 to 3 million litres in 2011. This is due to the growing complexity of the biologics developed, requiring more evolved production systems.

The CMO (contract manufacturing organizations) market for biologics was worth US$2.4 billion in 2007, with a growth rate of 14%. This growth rate was expected to remain constant in 2008 due to pharmaceutical industries outsourcing their bioproduction of commercial lots in order to reduce costs. AstraZeneca, GlaxoSmithKline, Bristol-Myers Squibb, Sanofi-Pasteur and Pfizer are already externalizing part of their production. The main biologics produced by CMOs are monoclonal antibodies, recombinant therapeutic proteins, vaccines and, in a more limited quantity, gene therapy vectors.

The other market segments being still in their infancy, production capacities are very limited and it is difficult to evaluate them. However, these emerging new disruptive treatment classes are considered as the (very long-term) future of medicine. For example, the stem cell therapy market is estimated to grow from 300$ million in the US to US$2.3 billion in 2012 and US$8 billion in the US in 2016. Current growth is approximately 100% a year.

Regarding gene therapy, the numerous ongoing clinical trials (200 in Europe), including 5 Phase III clinical trials for oncology (in Europe) push analysts to predict a fast growing market to reach US$5.3 billion in 2011. Around 50 potential viral vector manufacturers for gene therapy have been identified in EU (40%) and US (60%). In Europe these manufacturers are almost all private companies whereas in US half of them are structured academic platforms.

Trends and Developments

Recombinant proteins

Among the recombinant proteins, the different market segments are evolving differently. The most mature segment is therapeutic proteins, however it is in its mature phase and its growth rate is decreasing (increase of 17% in 2005 and increase of 14% in 2006). The strong growth of the recombinant proteins market is mainly due to the growth of the monoclonal antibodies segment (increase of 21% in 2008) and, to a more limited extent, the recombinant and therapeutic vaccines segment (increase of40% in 2006).

77 IMS Health; phRMA; Fierce Pharma; Bioprocess Technology Consultants; *World gene therapy market research report*, Frost & Sullivan, May 2005; *Bioproduction 2008, Etat des lieux et recommandations pour l'attractivité de la France*, Développement & Conseil, 2008

Regarding the production of these recombinant proteins, the following factors are impacting its development:

- The restructuring of pharmaceutical laboratories is leading to the outsourcing of bioproduction to CMOs, as biologics suffer from very high production costs compared to small molecules.
- The very favourable political context in Asia, linked with strong political will to develop significantly biotechnologies on the long term, is facilitating the implantation of new bioproduction facilities. As a result investments in Europe are diminishing in the favour of investments in South Asia.
- As mentioned before, the growing complexity of the biologics developed, requiring more evolved production systems.
- The development of biosimilars in bringing new entrants into the market (generic companies).

Important International Market Participants

Recombinant proteins

5 types of actors are present on the GMP bioproduction market of clinical and commercial lots:

- Public bioproduction platforms (small production of clinical lots for public laboratories and start-ups)
- Biotech companies (usually only large biotechs with products on the market have bioprocessing facilities)
  Large biotechs market leaders (revenues in 2007): Amgen ($14.7 billion), Genentech ($11.7 billion), Novo Nordisk ($5.89 billion), Biogen Idec ($2.6 billion), Genzyme ($2.2 billion)
- Pharmaceutical laboratories (large capacities for commercial lot production)
  Pharmaceutical laboratories market leaders (revenues from biologics in 2007): Johnson & Johnson ($6.8 billion), Eli Lilly & Co ($3.2 billion), Sanofi-Aventis ($3.2 billion), Abbott ($3.1 billion)
- Manufacturers of biosimilars (large capacities for commercial lot production)
  Sandoz, Biopartners,
- CMOs = Contract Manufacturing Organizations (small capacities only for clinical lots and orphan drug commercial lots or large capacities for commercial lot production)
  CMO market leaders Boehringer-Ingelheim, DioSynth, Lonza, DSM

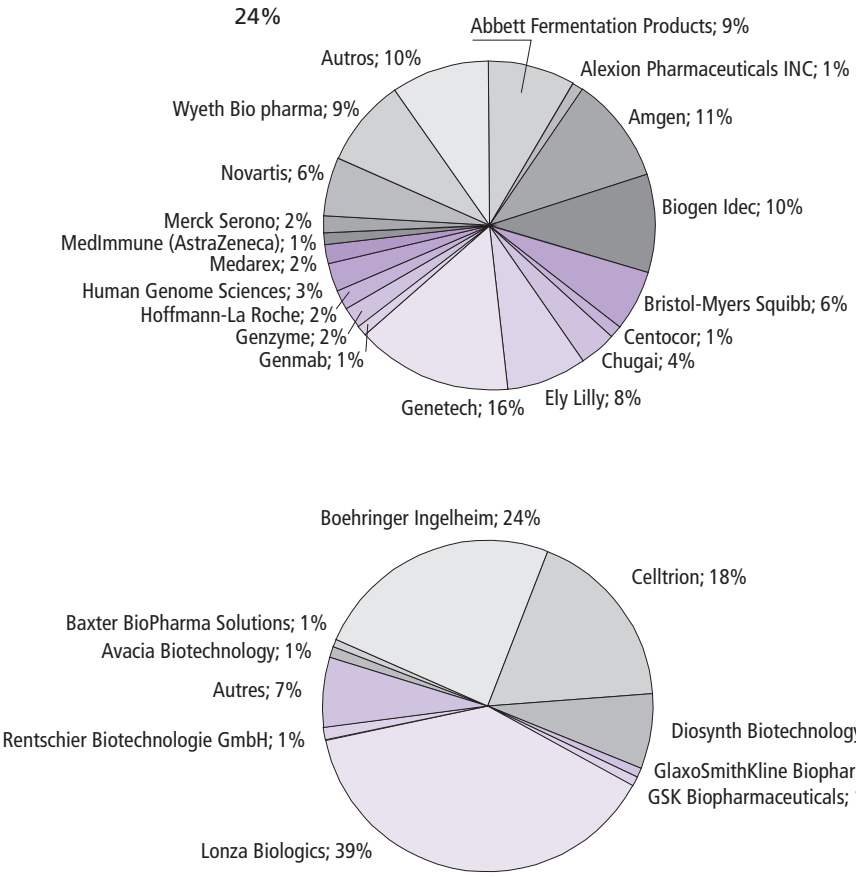


Figure 25: Pharmaceutical laboratories and large biotechs CMOs (excluding vaccines and biosimilars)
(Source: Conseil & Développement, 2008)

Production in transgenic animal

As production in transgenic animal is an emerging market, main actors remain research institutions in partnership with biotech companies (e.g. Hematech, GTC Biotherapeutics).

Stem cells

Largest Stem cell therapies suppliers in the US (ranked in the order of revenues generated from the sale of stem cell therapies or related products):

- Blackstone Medical (a subsidiary of Orthofix Inc)
- Osiris Therapeutics
- NuTech Medical
- ViaCell
- Aastrom Biosciences

Gene therapy

In Europe, 18 CMOs have been identified for the production of viral vectors (some of which are also biotechnology companies developing gene therapy products). Half of these CMOs are located either in UK and Scotland or in Germany. Main European actors are:

- AMT therapeutics (Netherlands): the company created in 1998 employs 40 people and produces baculovirus (adeno-associated virus) vectors for its own gene therapy products for rare disease. It has a 200m² GMP facility and is developing 400L bioreactors.
- Molmed (Italy): the company created in 1996 employs 99 people and produces lentivirus vectors and recombinant proteins for oncology, HIV and rare disease. It is also involved in cell therapy. It has 900²m GMP facilities and a mixed product/service business model.
- Oxford Biomedica (UK): the company created in 1995 employs 75 people and produces lentivirus and poxvirus vectors for oncology and neurology. Its business model is based on products, licensing and partnerships.

It may be noted that most of these companies are also involved in the production of stem cell products (e.g. Angel Biotechnology).

Time to Market

- The construction of a bioproduction unit for commercial lots of recombinant protein requires 4 to 6 years from the beginning of the construction project to the qualification of the facility for operation and represents an average investment of €150 to €800 million.
- For viral vector production, 8 to 12 months are necessary to go from research to market, the most critical step being the transfer from a research protocol to GMP large-scale production.

Identified Bottlenecks

Recombinant proteins

- Growing delocalization strategies for the commercial production

Gene therapy

The following challenges impact the development of gene therapies, and therefore the wide-scale production of vectors:

- Little success met in clinical trials to date.
- Very high expectations of regulatory authorities regarding surveillance and follow-up of gene therapy trials.
- Negative perception from the public and need for information.
- Technical constraints and sanitary risks linked to the use of viral vectors.
- Potentially high prices of treatments based on gene therapy.
- Absence of standardized vector production standards.

In this context bioproduction of vectors remains limited to the research and clinical trials markets.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for the Future Implementation[78]
Examples of largest companies and description of their activities in the field

- LabAs: The Tartu-based company established in the early 1990's produces, purifies and labels custom mono- and polyclonal antibodies for biotechnology companies and research institutions. It is mainly a service-based company but has participated in research and development projects, connected with gene transfection into in vitro cultivated cells.
- AS Kevelt: The Tallinn based company has been producing pharmaceuticals for more than ten years, starting with chemical entities in GMP conditions. Today, the company is also involved in the production of biologics (e.g.: Eicosanoid hormones) however in non-GMP conditions, therefore targeted for research purposes.
- Icosagen Cell Factory OÜ (subsidiary of the Icosagen AS groups, the non-medical diagnostic branch of the former Quattromed group): The Tartu-based company has developed a proprietary expression system based, consisting of a plasmid and a stable mammalian cell line, for the production of recombinant proteins, humanized monoclonal antibodies and virus-like particles for preclinical research use, and for the development of cell-based assays. The company offers small capacity CMO services (several up to 1 litre spinners and a 3 litre vessel fermentation system) but the process is claimed to be able to upscale. It also offers to license its proprietary technology (any lab with DNA cloning and cell culture facilities can use the company's technology). The targeted market is the preclinical lot market for large biotechs and pharmas developing biologics.

The group is also producing recombinant proteins as research tools, cell lines and expression vectors; monoclonal antibodies; enzymes (DNA polymerase and cystein protease).

- Cell In: The Tallinn-based company is building a GMP manufacturing plant to produce stem cells for clinical research purposes. The facility will be based on an innovative approach enabling faster cell propagation time. A patent has been filed on this approach. The facility is being built for Estonian research purposes as well as for foreign use. Interest in service and licensing of the technology has already been shown by foreign companies.
- Competence Centre for Cancer Research: The competence centre is involved in several projects regarding the development of new generation cancer drugs and the development and the implementation of new technological platforms for early diagnosis and prognosis of cancer, in partnership with several institutions and companies (Tallinn University of Technology, North Estonia Medical Centre, Trial Form Support TFS AB, CeMines Estonia Ltd, Cambrex Tallinn Ltd, Kevelt Ltd, Celecure Ltd, Inbio Ltd, University of Tartu, Protobios Ltd., EPhaG Ltd., Quattromed HTI Laborid Ltd. and Baltic Technology Development). It has several ongoing projects concerning bioprocessing, in particular, a project on novel growth factors in the production of therapeutic proteins in mammalian cells.

It must be underlined that regarding bioproduction for Estonian products, there are few products today that are mature enough to require GMP bioprocessing facilities.

Supporting Research and Development for the Field
Numerous research and development projects have been identified in the field, including:

- Transgenic animals: 2 large research projects are ongoing to develop transgenic cows for the production of human therapeutic proteins in bovine milk (new research and development area, started in 2008). This research is conducted by Estonian University of Life Sciences, Institute of Veterinary Medicine and Animal Sciences, Competence Centre on Reproductive Biomedicine and Reproductive Biology, Institute of Technology of the University of Tartu, in partnership with Estonian Animal Breeders Association, Tartu Biotechnology Park, LanLab OÜ and foreign partners (COST GEMINI, University of Munich, BioTalentum Ltd). To date, embryos integrating existing therapeutic protein genes have been produced (but no calves yet).
- The effect of novel growth factors to productivity of therapeutic proteins in mammalian cells (Development of a technological platform for optimized laboratory scale cultivation of different mammalian cells: Use of selenium-enriched yeast extract) – among others: CCCR, Department of Gene Technology, Faculty of Science, Tallinn University of Technology, 2008-2011.
- Optimization of culture conditions specifically for NK cell expansion in connection with stem cell transplantation – CCCR, University of Tartu, Faculty of Medicine, Department of Haematology and Oncology; in collaboration with Karolinska Institute & Avaris AB, 2007-2010.

Other than companies, examples of which are mentioned above, research institutions involved in bioprocessing have been identified:

- University of Tartu, Faculty of Science and Technology, Institute of Technology,
- Estonian Biocentre,

78 Company websites www.estonianbiotech.ee, ETIS database; Estonian, European and US patent offices; Interviews

- Tallinn University of Technology, Faculty of Science, Department of Gene Technology,
- University of Tartu, Faculty of Medicine, Department of Haematology and Oncology,
- Estonian University of Life Sciences, Institute of Veterinary Medicine and Animal Sciences.

Finance & IP situation

There has been significant governmental support in the domain; of the 21 projects funded by EAS in the first half of 2009, at least 5 are related to bioprocessing.

A significant number of patents related to bioprocessing have been identified:

Different patents have been published in 2009 for the mammalian expression system related to Icosagen (Episomal vector and uses thereof, WO 9724451, Vectors, cell lines and their use in obtaining extended episomal maintenance replication of hybrid plasmids and expression of gene products, WO 2006084754)

1 patent concerning SE-YE (The use of extract of selenium-enriched yeast (Se-YE) in mammalian cell culture media formulations; Owner: Cambrex Tallinn AS, Celecure, Competence Center for Cancer Research, Inbio, Kevelt AS, North Estonian Regional Hospital, Protobios LLC, Tallinn University of Technology; Authors: Monika Drews, Reet Rumvolt, Karoli Voodla; Priority number: US61/059874; Priority date: 09.06.2008)

Three inventions in the field of optimization of culture conditions:

- Method for the genetic activitation of cells and uses of said cells; Owner: Avaris AB; Authors: Alar Aints, Sirac Dilber, Kyriakos Konstantinidis; Priority date: 02.07.2004
- Selection marker for rapid selection of human cells; Owner: Avaris AB; Authors: Alar Aints, Alexandra Treschow, Sirac Dilber; Priority number: 0300412-4; Priority date: 14.02.2003
- Cell Culture vessel; Owner: Competence Center for Cancer Research; Authors: Alar Aints; Priority number: 0014/07PV; Priority date: 03.04.2007

Summary

A potent short- to mid-term research and development opportunity for Estonia

Strengths Existing research activity in several academic institutions and private companies on several different themes. Existing companies on mixed CMO service and product development business models in the field. Involvement of competence centres. Several filed and published patents including in the US. On-going project of construction of a GMP facility for stem cell production, based on a proprietary technological innovation. Foreign interest shown for in-licensing opportunities of developed bioprocessing technologies.	Weaknesses Current business mainly oriented on chemical entities. Limited number of bioproduction facilities with limited capacities. Limited internal need due to the limited number of biologics at a sufficient maturation level to require mid to large production capacities (linked with the limited phase I and phase II activity in Estonia).
Opportunities Rapid development of biologics, representing today 30% of the molecules introduced in the market recently (and that share is growing). Promises held by gene and cell therapies as disruptive new types of treatments, likely to represent tomorrow's medicine. Evolution of biologics to more and more complex molecules, requiring new more elaborated production systems to be developed.	Threats Regarding commercial production of recombinant proteins, growing delocalization strategies towards developing countries (especially in South East Asia). Strong political will to develop biotechnologies in general, and cell and gene therapy in particular, in South East Asia (e.g. China, Singapore) leading to high unbalanced conditions. These countries offer attractive economic measures and simpler regulatory contexts. Limitations of the development of cell and gene therapy due to, respectively, ethic concerns and limited success met in clinical trials today. Critical step linked to scaling-up. Existing high-competition of actors that are a step ahead (including large actors like the pharmaceutical companies).

Conclusion about the Potential for Estonia

Research activity exists in the field of bioprocessing, in research institutions as well as in companies, common projects being led between both. This activity has brought to several inventions and patent applications have been filed (and published). Some companies are already providing services in the field and the construction of a GMP facility for stem cell production is ongoing. However, these initiatives remain early stage in comparison to the global context, especially relatively to commercial production of recombinant proteins. The economic potential of this activity must be evaluated in the light of the numerous well-established existing actors, including very large players and the complexity related to up-scaling bioprocesses. Furthermore, due to strong political will and lower costs there is a trend for delocalization of such large-scale production to South-East Asia.

On the other hand, high added-value projects for the development of technological advances hold potential especially in emerging fields, such as gene or cell therapy products. Up-scaling can be considered in partnership with larger actors. However, it must be noted that the field in Estonia is still at an early stage and will require further efforts.

1.7 National Security

1.7.1 Biodefense

Introduction

Definition of the Field[79]
Biodefense is a somewhat abstract concept. However, most often it is referred to as local, sometimes also military, measures to restore biosecurity. Biodefense can be understood as an anti measure for/as a protection measure from bioterrorism. In recent years, bioterrorism has been under more intense focus. The world is largely unaware of, and hence largely unprepared for various bioterrorist attacks. Biotechnology is undergoing rapid evolution and hence biodefense is also becoming a more important research area of biotechnology.

Though no terrorist action has happened to date in Europe, the ones that happened in US in 2001 have touched Europe through the fear and false alerts that they generated. Today we do not know if this threat is true, when it will occur or what will be the pathogen agent used. The industrial market is therefore very difficult to characterize. The list of pathogen agents at risk is not exhaustive, because the advances of science and technology can generate new infectious agents or variants. The ways of dissemination are mainly aerosols and water.

According to David Relman (Stanford University, The New England Journal of Medicine, January 2006), "For the vast array of other potential threats, however, we should invest even more in flexible, dynamic defenses, which will rely on integrative science, new insights into biologic systems, and advancing technology. We need methods and technologies that can generate effective diagnostics, therapeutics, and prophylactics against a new or variant infectious agent within days or weeks after its characterization."

The biodefense market appears restrained and risky, because needs are materialized today only with the military, with a unique client, the government. The uncertainties of the market are linked to the specificities of the products to develop: sturdiness, portability, stability, and constraining regulations.

However, as the BIO2007 convention showed, a large number of biotechnological companies are present on these niche markets.

Examples of Products and Services[80]
Biological detection systems are currently under research and still in early development stages. There are some commercially available devices that have limited utility (detecting only a small number of agents) and are generally high cost items. Because commercially available biological warfare (BW)[81] detection systems and/or components exhibit limited utility in detecting and identifying BW agents and are also costly, it is strongly

79 EY Internal experts on biotech; University of Stanford, The New England Journal of Medicine, January 2006; Interpol on Bioterrorism http://www.interpol.int/
80 *Enforcement and Corrections Standards and Testing Program (An introduction to Biological Agent Detection Equipment for Emergency First Responders report)* National Institute of Justice Law
81 *Biological warfare – the use of bacteria or viruses or toxins to destroy men and animals or food*

recommended that first responders be very careful when considering the purchase of any device that claims to detect BW agents[82].

The main detection systems and products for biologic agents that have been identified are:

Point Detection Technologies

Point detectors are those sensors that must be in the aerosol plume or have the suspect biological agent introduced into/onto them for sensing.

Trigger/Cue (Non-specific Biological Agent Detectors)
Trigger technology is the first level of detection that determines any change in the particulate background at the sensor, indicating a possible introduction of biological agents.

Particle Measurement
One technique used for non-specific detection is counting the relative number of particles in specific size ranges (typically 0.5 mm to 30 mm).

- Aerodynamic Particle Sizing (APS) – The particle-laden air stream is drawn into the APS device through a flow nozzle, producing a controlled high-speed aerosol jet.
- High Volume Aerodynamic Particle Sizer (HVAPS) – The HVAPS passes an accelerated, concentrated air stream past a laser-based particle counter to obtain aerosol particle size distribution and concentration.
- Met-One – The Met-One is a compact, low-power aerosol particle sizer and counter about the size of a large, hand-held calculator.

Fluorescence Methods
Fluorescence approaches involve excitation of molecular components of a material with light, usually in the ultra violet (UV) region of the spectrum.

- Fluorescent Aerodynamic Particle Sizer (FLAPS) – FLAPS is an Aerodynamic Particle Sizer (APS) that has been modified to include an additional laser (blue or UV wavelength) that provides for aerosol particle fluorescence in addition to standard particle size information.
- Biological Aerosol Warning System (BAWS) – The BAWS uses a micro-laser-based system that analyzes two biological fluorescence wavelengths to determine if an unusual biological event is happening.
- Portable Biofluorosensor (PBS) – The technique uses UV light from a xenon flash lamp to excite airborne aerosols and aerosols dissolved in water.
- Single-Particle Fluorescence Counter (SPFC) – developed by the Naval Research Laboratory (NRL), it employs continuous airflow across a 780 nm laser-diode beam, resulting in light scattering from individual aerosol particles in the air.

Samplers/Collectors

Since an extremely low airborne concentration of biological agents can be difficult to detect but still cause severe effects, a device to concentrate particles/aerosols in the air stream is needed. A collector/concentrator samples the atmosphere and concentrates the airborne particles into a liquid medium for analysis.

Viable Particle Size Samplers (Impactors)
A conventional impactor operates by accelerating an air stream of particles through a nozzle and diverting the air stream against an impaction plate maintained at a fixed distance from the nozzle.

Virtual Impactors
A virtual impactor is similar to a conventional impactor but uses a different impaction surface. The flat plate of the conventional impactor is replaced by a collection probe, and the larger particles penetrate the collection probe instead of striking a flat.

- Liquid Sampler (PEM-0020) – with carousel is manufactured by Power Engineering. The device uses virtual impaction to collect and concentrate airborne particles onto liquid film.
- BioVIC Aerosol Collector – developed by MesoSystems Technology, Inc., serves as a front-end air sampler for biological detection systems. It is an impactor that pre-concentrates the air stream, capturing large numbers of particles either into a small volume of liquid, into a small air stream, or onto a solid surface for delivery into the sensor.

82 *Enforcement and Corrections Standards and Testing Program (An introduction to Biological Agent Detection Equipment for Emergency First Responders report)* National Institute of Justice Law

Cyclone Samplers

- Interim Biological Agent Detector System (IBADS) – was initially developed for the Navy. It uses a wetted-wall cyclone to collect the aerosol particles into an aqueous sample.
- Smart Air Sampler System (SASS 2000) – is a device that has been independently developed by Research International and also uses wetted-wall cyclone technology. This hand-held device can operate on battery power.
- Portable High-Throughput Liquid Aerosol Air Sampler System (PHTLAAS) – is a small hand-held device that uses technology similar to the wetted-wall cyclone technology. This instrument concentrates the contaminants found in a large volume of air into a small volume of liquid for ultrasensitive semi-quantitative detection.

Hand-Held Sampling Kit

- Department of Defense Biological Sampling Kit (DoD BSK) – is a pre-packaged kit containing a panel of eight hand-held immunochromatographic assay (HHA) devices (i.e., able to identify simultaneously up to eight different biological agents), a dropper bottle of buffer solution, two sterile cotton-tipped swabs, and an instruction card.

Hand-Held Sampling Device

- BioCapture BT-500 Air Sampler – was developed by MesoSystems Technology, Inc., and incorporates the BioVIC Aerosol Collector, also developed by MesoSystems Technology, Inc. It is a hand-held, battery-powered air sampler that collects airborne samples for quantifying concentration levels.

Detectors

Wet Detection (Flow Cytometry)

Cytometry is the measurement of both physical and chemical characteristics of cells. Flow cytometry (widely used as a wet detector for biological agents) uses the same technique as cytometry but makes the measurements of cells or other particles present in a moving fluid stream as they pass through a testing point.

- Los Alamos National Laboratory (LANL) Flow Cytometer – employs a green (HeNe) laser diode. Particle size is measured by two light-scatter detectors, and fluorescence is measured by two photomultiplier tubes.
- B-D Flow Cytometer FACSCount – manufactured by Becton Dickenson, employs a direct two-colour immunofluorescence method and uses a green (HeNe) laser.
- B-D Flow Cytometer FACSCaliber – manufactured by Becton Dickenson, is a four-color Modular Analytical Flow Cytometer that uses a 15 mW air-cooled blue argon-ion laser and a red laser diode. The FACSCalibur also has an optional sorter.

DRY detectors (Mass Spectrometry)

Mass spectrometry (MS) is a micro-analytical technique that requires only a few nanograms of analyte to obtain characteristic information on the structure and molecular weight of the analyte.

- Pyrolysis-Gas Chromatography-Ion Mobility Spectrometer (PY-GC-IMS) – combusts, or pyrolyzes, the biological particles. The biological pyrolysis products are then separated using gas chromatography.
- Matrix-Assisted Laser Desorption Ionization-Time of Flight-Mass Spectrometry (MALDI-TOF-MS) – is a variation of mass spectrometry that attempts to use a more gentle method of ionizing the suspect biological agent than pyrolysis to allow identification of the agent rather than just broad characterization.
- Chemical Biological Mass Spectrometer (CBMS) – uses a multistage process to analyze aerosols for biological content and categorize any biological constituents.

Identifiers (Specific Identification Technologies)

Identifiers are those components/instruments that are able to identify the suspect biological agent to the species level (for cellular and viral agents) and toxin type.

Immunoassay Technologies

Disposable matrix devices are often referred to as tickets or kits. They usually involve dry reagents, which are reconstituted when a sample is added.

- Hand-Held Immunochromatographic Assays (HHAs) – are simple, one-time-use devices that are very similar to the urine test strips used in home pregnancy tests. There are currently 10 live agent assays in production, four simulants, and five trainers (only saline solution is needed to get positive results).
- BioThreat Alert™ Test – The BTA Test Strips – Immunochromatographie technique uses monoclonal antibodies that fix selectively to the substances to detect: anthrax, ricine, toxine botulique, entérotoxines, peste, tularémie, brucellosis.
- Sensitive Membrane Antigen Rapid Test (SMART) – is a ticket-based system for detecting and identifying multiple analytes. The core chemistry approach detects antigens in the sample by immunofocusing colloidal gold-labelled reagents (levelled antibodies) and their corresponding antigens onto small membranes.

- Bi-Diffractive Grating Coupler (BDG) – an optical transducer that is being developed by Battelle Memorial Institute and Hoffman LaRoche. This device takes advantage of a phenomenon linked with one of the two components of a polarized light wave.

Nucleic Acid Amplification
Nucleic acid amplification may be used to help detect the presence of DNA or RNA of bacterial and viral biological agents (nucleic acid amplification cannot directly detect the presence of the toxins themselves).

- Mini-PCR (Ten Chamber PCR) – is an instrument that has been developed by Lawrence Livermore National Laboratory (LLNL) and represents one of the first attempts to get gene-based identification technologies in a field-useable format.
- LightCycler™ – is developed by Idaho Technology, is a thermal cycler that uses a unique built-in fluorimetric detection system with specially developed fluorescent dyes, as well as Taq-man technology, for on-line quantification and amplification products. It is being manufactured under license by Roche Diagnostics.
- Ruggedized Advanced Pathogen Identification Device (RAPID) – from Idaho Technology, is a rugged, portable field instrument that integrates the LightCycler™ technology. The RAPID can run a reaction and automatically analyze the results in less than 30 min.

Standoff technologies

Standoff systems are designed to detect and identify biological agents at a distance away from the aerosol/plume or from the detector system, before the agents reach the location of the system. Standoff systems do not utilize a trigger/cue, collector, or detector but use a bright light source, such as a laser for detection of the biological agents.

- Compact LIDAR – is a system that has been in development at Soldier Biological and Chemical Command (SBCCOM) and Edgewood Chemical and Biological Center (ECBC) since 1996.
- Hybrid LIDAR is a system under development by the Electro Optics Organization Inc. (EOO) and Stanford Research Institute (SRI), under the sponsorship of the Defense Advanced Research Projects Agency (DARPA).
- MIRELA is an IR LIDAR that is being collaboratively developed by SBCCOM and France. The system was originally developed for standoff detection of chemical clouds but is now being evaluated for bio-aerosol detection.
- MPL 1000 and MPL 2000 are commercially available IR LIDAR systems (manufactured by Science and Engineering Services, Inc.-SESI) originally developed in collaboration with NASA Goddard Space Flight Center for monitoring atmospheric cloud and aerosol structures.
- Long-Range Biological Standoff Detection System (LR-BSDS) can detect aerosol clouds up to 30 km from the detector from an airborne platform, specifically a helicopter. This system uses pulsed laser beams in the near-IR regime of the optical spectrum (1 mm) to detect these clouds.

Passive standoff technologies

Passive standoff detection systems rely on the background electromagnetic energy present in the environment for detection of biological agents. Typically, these systems look at the mid-IR (3 m to 5 m) or far-IR (8 m to 12 m) region of the spectrum for agent signatures.

International Business Potential

International Market Size and Growth[83]

Biodefense strategies in Europe

In response to this threat the European Union, through a frame decision of the council against terrorism dating from 13 June 2002, has decided to ameliorate the plans of fighting against biologic, chemical and radiological agents. The European Centre for Disease Prevention and Control has defined in its strategic plan measures in the domain of biosecurity. The 7th PCRD (2007-2013) also proposes calls for projects in this domain. These measures are in a more global context of fight against emerging infections, multi-resistant bacteria infections, or infections due to modified bacteria, escaped from their laboratories intentionally or not.

Current international market and most important market players

The current techniques used are mostly based on RNA and DNA detection. For instance, Idaho Technology, a well-established American Biotech company, has developed a set of portable real time quantitative PCR instrument based on Lightcycler technologies to detect bacteria and viruses.

83 European Centre for Disease Prevention and Control http://www.ecdc.europa.eu/; *Enforcement and Corrections Standards and Testing Program (An introduction to Biological Agent Detection Equipment for Emergency First Responders report)* National Institute of Justice Law; Interpol on Bioterrorism http://www.interpol.int/

Although developers of biodefense tools represent a wide range of scientific disciplines that have always been served by the life science industry, their newly increased purchasing power and urgency of their work distinguish them from other customer groups in the market. Biodefense researchers are using the existing products of their supplies, and when necessary, easily adapting them to their applications indicating that suppliers should have little difficulty in leveraging their existing product portfolio in this market. Products from well-known companies, such as Invitrogen, Sigma-Aldrich, Bio-Rad and Qiagen are widely used in biodefense laboratories despite the fact that few of their products are specifically designed for biodefense research. Since the ability to effectively combat bioterrorism largely depends on the information generated by biomedical research on disease-causing microorganisms and the immune system's response to them, nearly US$1.6 billion was allocated in 2006 to the National Institutes of Health (NIH). This budget is supposed to support basic research on potential agents of bioterrorism, such as anthrax or smallpox, as well as the development of vaccines, diagnostic tests and therapies to detect and counter the effects of a bioterrorist attack.

Main Industry Drivers

- Low financial requirement for development (compared to healthcare applications);
- Low regulatory requirements for development (compared to healthcare applications);
- Developing public and regulatory concern for bioterrorism and public pandemics leading to an increasing number of public sanitary safety politics;
- Availability of public funding for developments of such tools, Solvability of the defence sector (US).

Identified Bottlenecks

- Number of pathogens under study today;
- At the same time, continuous possibility of generation of new pathogen agents or variants (leading to large unpredictability);
- Trend to limit military expenditures (EU);
- Requirement for sturdy, portable and stable tools whilst existing pressure on fabrication costs;
- Growing Regulatory hurdles (FDA, EPA, FTC, CPSC);
- Societal implications of nanotechnology;
- Legal and ethical challenges linked with the "control and monitoring" aspect of biodefense.

Important International Market Participants

Some international market participants that are active in the field are Idaho Technology, Invitrogen, Sigma-Aldrich, Bio-Rad, Qiagen and MesoSystems Technology.

Assessment of Estonian Potential

Existing Production and Companies with the Potential for the Future Implementation

There is no identified activity in this field in Estonia.

Advantages, competences and resources in healthcare diagnostics (supported by Estonia's strengths in genetics and bioinformatics) and emerging activity in environmental monitoring tools could be easily transferred to the biodefense sector. However, taking into account the limited number of clients and the existing global competition, the economic interest of this should be further assessed and the development of this field could be considered as a second-line opportunity. The development time of this business field will most probably be limited more by building capacities and making a name in the biodefense sector than by the technological development time (2 to 3 years).

1.8 Conclusion: which fields have the highest potential for biotechnology uptake in Estonia?

The following figure gives a global overview of the business field positioning and their potentials for Estonia. On the horizontal axis value and market potential for Estonia is evaluated and on vertical axis Estonia's performance is mapped. Under the Estonian performance critical mass of scientists, research and applications maturity was analyzed. Under value and market potential for Estonia, international and local market size as well as international competition and barriers for entering the market were considered. The positions on the matrix were developed in comparing different business fields to each other, meaning that business fields were positioned according to qualitative estimations. The conclusions of the business fields presented after the matrix figure summarize the rationale for each business field to be positioned as it is, the analysis of the business fields being described in more detail in the first chapter of the report.

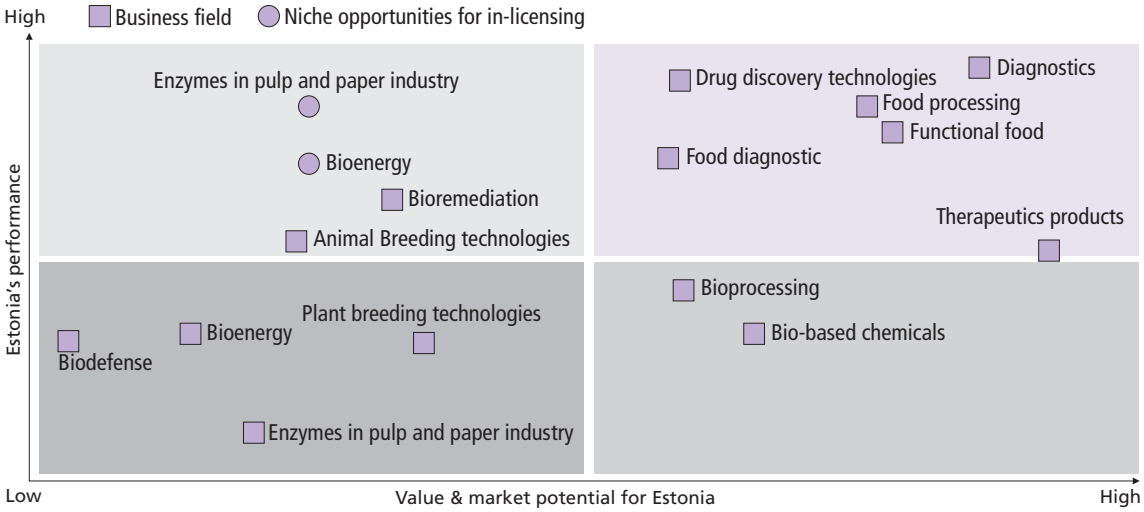


Figure 27: Estonian potential in different business fields

The results showed that most potential business fields in Estonian biotechnology are related to food and healthcare sector. In short- to mid-term perspectives good opportunities in the field of diagnostics, drug discovery technologies, food processing, functional food as well as food diagnostics and safety were identified. In long-term perspective diagnostics and therapeutic products were identified as promising potential business fields. Additionally to that rather feasible niche opportunities were identified in the fields of animal breeding technologies and enzyme use in paper and pulping industry. The following section elaborates on each business field in more detail:

Priority Targets

Functional Food (FF) Business Field:

The functional food business field, and more generally, the food industry represent a real opportunity for growth in Estonia. The country can rely on a critical mass of functional food industry companies having already partially turned into a knowledge-based economy system. This field is supported by a strong and applied research community, including two competence centres, with a primary experience in deal making with the industry. The market size for functional ingredients and functional food is remarkably high and quickly growing. Although the market is dominated by big players, the current need of these big players for novel innovative ingredients is obvious and results in the increasing number of alliances and license agreements between big players and small companies, or even applied academic research, leading to major opportunities for Estonia. The remaining challenges regarding this business field will be to further develop the practice of patent filing of inventions, with more numerous patent skills at both academic and industry level, as well as to establish the right proof of concept corresponding to the acceptable industrial in-licensing standards and to license out the innovation through solid and experience business development skills.

Food Processing (FP) Business Field:

The food processing industry is clearly a more mature business field in Estonia, with critical mass at both industry and academic levels, which need to be supported to further turn into a sustainable business field using biotechnologies on a regular basis. Companies and institutions have started to integrate the central role of patent filing and prosecution as a key success factor and this has to be further supported. Both processed and packaged food markets as well as the industrial food enzyme market are considered as huge markets with significant constant growths. These markets lead to significant amount of short-term in-licensing opportunities for Estonia with food enzymes or food processing technologies to boost traditional industry towards new innovative products on the one hand, and mid-term innovative processed product development opportunities for further commercialization at both national and international levels on the other hand.

Food Diagnostics and Safety (FD) Business Field:

The food diagnostics business field is in between the food industry business and the diagnostics tools and technologies business, both of them being real strengths in Estonia. On the one hand, diagnostics tools and technologies bring technological support to accelerate the applicability of such technologies to food industry and to help overcome bottlenecks such as integration of data (bioinformatics), standardization and development of portable systems (biosensors, lab-on-chip). On the other hand, the food diagnostics field benefits from the growing safety concerns of the population and regulatory authorities about the quality and healthy nature of current processed food as well as from the growing consumption of fresh fruits and vegetables.

This convergence represents a good opportunity to build upon existing strengths to develop and build a new emerging and promising business field on a solid basis.

Therapeutic Products Business Field:
This field can be considered as a high added value, long-term opportunity for Estonia as long as this field is only built upon cutting edge, new classes of products (there is very limited interest in terms of differentiation for "me better" or "me too" therapeutic products taking into consideration the massive and highly active competition from large international companies and start ups). Indeed, a critical mass in this field does exist at both industry and academic levels with the emerging awareness of the importance of industrial property, the support from internationally recognized opinion leaders and the important number of projects being submitted or ongoing. However, the long-term characteristics of this field reinforce the crucial need to secure early-stage therapeutic projects through industrial property, licensing and technology transfer and early development best practices (aligned with industrial standards) through a long-term and strong support for cutting edge solutions.

Diagnostics Business Field:
The diagnostics field is certainly a very potent short- to mid-term opportunity for Estonia with long-term perspectives as well. The strong critical mass at industry and academic levels, supported by internationally recognized key opinion leaders and an important number of projects, is reinforced by the international context of deep shift in the healthcare management from pure curative solutions to prevention through early diagnosis and therapeutic monitoring in all major and minor therapeutic areas (central nervous system, oncology, cardiovascular, infertility, autoimmune diseases). This field even benefits from the strengths of Estonia in bioinformatics and genetics to overcome bottlenecks such as integration, treatment and interpretation of the generated data and standardization.

Drug Discovery Technologies Business Field:
Even though this field is not the largest in value and volume, however high and growing, this field is probably one of the shortest terms, strongest and most adapted biotech business fields in Estonia due to its positioning at the early stage level of innovation development, as well as its compatibility with mixed services and product development business models. This field is strongly supported by an applied research workforce in bioinformatics, genetics and physics, as well as a critical mass in fundamental research. This field is relatively well established (in terms of industrial property, licensing or commercialization) to allow the sustainability of the system.

Niche opportunities / Quick Wins (short-term)
Bioremediation Business Field:
The bioremediation business field is essentially represented at the academic level as no company has been identified as especially involved in bioremediation. However, this field may well benefit from other complementary competences that significantly exist in Estonia such as microbiology, metagenomics, bioinformatics, environment monitoring and management. In addition, this field is strongly supported by the government as well as the EU and at the same time, even emerging countries are feeling more and more concerned by sustainable development. At international level, bioremediation is an existing but still largely innovative industry quickly developing. Despite obvious technological challenges such as the scale up of a particular technology (e.g. metagenomic approach in environmental monitoring) to field operations, this field could be a short- to mid-term opportunity for Estonia as there are already applied research projects on microbial strains for waste management and environmental monitoring ongoing, which could drive this sector at national level targeting both national and international markets.

Animal Breeding Technologies (ABT) Business Field:
The ABT sector is characterized by an existing, quite important and structured animal breeding system with existing research activities on biotechnological animal breeding (including transgenic animal creation, although not applied to agriculture). The existence of an Estonian diagnostics, genetics and bioinformatics workforce is synergistic with the potential to develop molecular marker assisted selection tools and services for animal breeding. This is even reinforced by the willingness of the European population for healthier food and agriculture environmental protection addressable through animal breeding. However, the complexity of the regulatory environment, the early stage of technological development of molecular marker assisted selection tools for animal breeding, as well as the difficulty to create a market positioning as a new entrant, lead to envisage the ABT business field as a niche opportunity. Development should be considered with the objective of marketing molecular marker assisted selection tools and high tech services in animal breeding for international markets, rather than creating transgenic animals for agriculture (transgenic animal creation for therapeutic molecule manufacturing purposes has been considered in the bioprocessing business field).

Niche Opportunity in the Paper and Pulp Industry

This field has to be considered rather as a good niche opportunity for the Estonian forestry sector, as neither academic or private research in this field nor existing or emerging biotechnology industry have been identified. Indeed, Estonia owns important forest resources and has currently a mature forestry industry which could greatly benefit from the acquisition of pulp and paper enzymes from international industries for the improvement of product quality and productivity of this industry in the short term as well as modernization and more knowledgeable industry with higher added value in the longer term.

Niche Opportunity in Bioenergy

Estonia may consider the bioenergy field as an opportunity for in-licensing existing patented technologies from other countries (USA or Western Europe for instance) for national or regional (e.g. Baltic countries) markets and energetic independency purposes only, the competition being too high in this field. Indeed, even existing Western European companies have difficulties in resisting the competition of US-based companies.

Mid- to Long-term Initiatives (Need to identify competitive advantages)

Bio-based Chemicals (BBC) Business Field:

This field can be set up on the basis of strong microbiology and genetics competences and large existing cellulosic national resources. The supporting technologies, enzymatic degradations of cellulosic feedstock, are common to this field and the bioenergy business field allowing focused and synergistic efforts while leading to very large and fast growing markets. This field even benefits from the sustainable development trend for more environmentally friendly and efficient processes in multiple industrial applications. However, this field being still at a very early stage of maturation and the international competition being rather high, it can only be considered as a long-term opportunity requiring further technological development to achieve cost efficient cellulosic feedstock transformation.

Bioprocessing Business Field:

This field is driven in Estonia by existing research activities both at industry and academic research levels leading to a promising potential of this area only if the efforts are exclusively focused on certain complex very innovative bioprocessing technologies such as stem cell production or cutting edge new bioprocessing solutions. Classical bioprocessing solutions for manufacturing services of antibodies or proteins should be left to emerging low labour costs countries such as China and India.

Secondary interest fields

Plant Breeding Technologies (PBT) Business Field:

The PBT business field in Estonia is mainly centred on competences in traditional breeding, plant molecular physiology, as well as genetics and virology. However, a scientific expertise is currently emerging in advanced breeding techniques and more particularly in molecular marker assisted selection. The global international environment of plant breeding is clearly dominated and driven by genetically modified organisms (GMOs), big companies and big countries being deeply involved. However, Europe is highly uncertain in terms of regulatory context for GMOs and the public is in general not supportive of such types of products, leading to a rather limited potential of GMO development and commercialization in Europe. Taking into account the specific development conditions needed in GMOs breeding (e.g. outdoors breeding), the concept of keeping the research in Estonia to commercialize outside of Europe has very limited possibilities of success. Therefore, this non-traditional PBT business field does not represent a priority for Estonia except the niche opportunity of molecular marker assisted selection that could be improved up to an excellence level able to be further commercialized at both national and international levels as high tech services.

Enzymes in Pulp and Paper (EPP) business field:

Due to the lack of identified academic or private research in this field as well as no existing or emerging biotechnology related industry, this field has to be rather considered as a good niche opportunity for Estonia in specific in-licensing cases.

Bioenergy Business Field:

This field is correlated with the massive and growing demand for renewable energy at international level. In Estonia, despite a critical mass of traditional biofuel energy industry (combustion system), a rather small workforce at both academic and industry level is concerned by biotechnology related biofuel. In addition, the incredibly high pressure from the US competition on this topic has resulted in a huge threat for well-established European companies and is therefore ever more threatening for the new entrant that Estonia might be. As a consequence, Estonia may consider this field as an opportunity for in-licensing existing technologies from other countries/companies (USA or Western Europe for instance) for national or regional (e.g. Baltic countries) markets and energetic independence purposes only.

Biodefense Business Field:
Biodefense is a field where no activity has been identified in Estonia. However, certain competences such as bioinformatics, biosensors, genetics and diagnostics, which are very strong locally, could easily be adapted to such topics. The strong international competition as well as the governmentally driven nature of this field leads to suggest that it is not a primary opportunity for Estonia, although it might be considered as an opportunity for political reasons.

Transversal conclusions:

In addition to business fields-related subjects, a couple of common points to each business field need to be underlined.

A certain level of awareness (depending on the fields) of the current challenges faced today by the biotech field is existing at both industry and academic levels and the willingness to overcome these barriers is an important driver for the Estonian biotech ecosystem. However, the whole Estonian biotech field is suffering from gaps preventing from moving towards a sustainable economically valid system.

There is a lack of company with strong industrial property status able to compete with the position of companies from Western Europe, North America and emerging countries leading to a very limited potential for export commercialization as well as restrictive use of non services business model.

A further lack of financial investment able to support product development (often linked to the need for more money) have the consequence of offering to Estonian Biotech companies the only solution of developing services business models limiting consequently considerably the potential of development of the industry biotech field.

At the institutional level, a lack of methodology in supporting biotech industry sector (specialized national authority for field selection and support) has as consequence to allow limited coordination of general efforts.

A limited workforce in every biotech sub-field is observed leading to the need for more specific trainings, additional graduate people including Ph.D. to support any growth of this field.

The lack of marketing, business development and licensing profiles with good understanding of industrial property issues processes and regulatory situation has also been identified requiring specific training or joined MBA.

2 Evaluation of the Estonian Biotechnological Research Areas

Methodology Behind Analysis

A total number of researchers directly linked to the field of biotechnology have been estimated as 300[84]. To come to the updated list on key players and research fields the Estonian Research Portal was used. The Estonian Research Portal concentrates information on research- and development institutions, researchers, research projects and various research results. The Estonian Research Portal is also an information channel for submitting and processing grant applications and for submitting and confirming project reports. This means that the portal includes a list of publications of the most active researcher in academic sector in Estonia.

The data for this survey was obtained on persons related to biotechnology and who have published articles in international publications classified as 1.1 (articles indexed by Thomson Reuters Web of Science and/or published in journals indexed by ERIH (European Reference Index of the Humanities) categories A and B. The classification of 1.1 is believed to characterize the sector-activities rather promptly, because of its science-intensity and hence the need to publish in top-level journals to become visible. Also, according to the Research Portal the major publishing activity of the field is significantly converged under the classification of 1.1. The database entailed 4039 such publications corresponding to 510 scientists.

Next, the publications were matched with ISI 2007 impact factors[85] and thereafter filtered with an IF equal to or greater than 4. IF 4 was used to ensure that journals behind the publications are TOP- journals, and thus research published in these magazines is really world-class research. After filtration 988 publications remained. For those publications "First or Last author" filter was used, which means that only these scientists and publications remained where the scientist was either the first or last author (leader of the research or leader of the laboratory). After the second filtration 158 top research leaders with 365 publications were left for further analysis.

These 158 research leaders and 365 publications were assigned research fields, therapeutic areas and potential application domains and maturity levels. Maturity was evaluated on scale 1 to 4:

- 1- Very fundamental – No specific application domain linked (e.g.: evolutionary genetics)
- 2- Fundamental transversal biological mechanisms
- 3- Description of a specific biological pathway
- 4- Research on products (drug development – applied bioinformatics tools)

The following chapter concludes the results of analysis described in this section. The chosen methodology is meant to obtain a general picture at a national level of the distribution of high quality scientific research competences in Life Sciences according to institutions and, more importantly, according to research fields and to the level of applicability to biotechnology domains.

This methodology does not represent an exhaustive listing of the quality of various scientists or research groups. For example, applied research is comparatively underrepresented in high impact factor journals (though it is present). In a similar manner, animal sciences and food may be underrepresented. Furthermore, it must be noted that the initial database may not be complete as publications are listed on a voluntary basis.

Existing research and development competences to support Business Fields have been studied in each of the fields. The following section comprises a more systematic review of existing top scientific leaders in Estonia.

Evaluation of the Estonian Biotechnological Research Areas

Journals and Institutions

The bibliometric analysis based on the ETIS database showed that the Estonian scientists related to the biotechnology, publish in the world's top journals. 158 scientists have published in journals which have impact

84 Fraunhofer ISI 2002, Estonian Biotechnology Strategy 2008-2013: 33

85 The impact factor (IF) is a measure reflecting the average number of citations to articles published in science and social science journals. It is a measure of importance of scientific journals, journals with higher impact factors deemed to be more important than those with lower ones. The impact factor was devised by Eugene Garfield, the founder of the Institute for Scientific Information (ISI), now part of Thomson Reuters. Impact factors are calculated yearly for those journals that are indexed in Thomson Reuter's Journal Citation Reports.

factors (IF-s) above 4, representing 270 different publications. Out of these publications 53 were published in journals with IF-s above 7, which implies TOP-quality world-class research being conducted in the field of biotechnology in Estonia. The TOP journals Estonian scientists have been publishing in are the following:

Table 4: TOP-journals in which Estonian scientists have published

	Jounal Title	*Impact Factor*	*Nr of publications*
1	Cell	29,887	1
2	Nature Reviews Immunology	28,3	1
3	Science	26,372	1
4	Nature Genetics	25,556	1
5	Chemical Reviews	22,757	1
6	Annual Review of Genetics	18,302	1
7	Trends in Cell Biology	13,527	1
8	Neuron	13,41	1
9	Molecular Cell	13,156	2
10	Genome Research	11,224	2
11	American Journal of Human Genetics	11,092	9
12	Nature Structural Biology	11,085	1
13	Molecular Psychiatry	10,9	1
14	Blood	10,896	1
15	Annual Review of Genomics and Human Genetics	10,722	1
16	Trends in Pharmacological Sciences	9,61	1
17	Proceedings of the National Academy of Sciences of the United States of America	9,598	10
18	PLoS genetics	8,721	1
19	EMBO Journal	8,662	2
20	Journal of the American Chemical Society	7,885	6
21	Human Molecular Genetics	7,806	1
22	Current Opinion in Chemical Biology	7,588	2
23	EMBO Reports	7,45	2
24	Arteriosclerosis Thrombosis and Vascular Biology	7,221	1
25	Trends in Endocrinology and Metabolism	7,195	1
26	Journal of the American Society of Nephrology	7,111	1
	Grand Total		53

It may be observed that these journals are related to a relatively broad range of research themes (genetics, molecular biology, neurosciences, biochemistry).

The scientists publishing in these TOP journals are related to 9 institutions as their primary institution (see table in appendix):

- University of Tartu (100 "top research leaders")
- Tallinn University of Technology (31 "top research leaders")
- Estonian Biocentre (11 "top research leaders")
- National Institute of Chemical Physics and Biophysics (9 "top research leaders")
- Tallinn University (2 "top research leaders")
- Celecure AS (1 "top research leader")
- FIT Biotech Oyj Plc (1 "top research leader")
- National Institute for Health Development (1 "top research leaders") Protobios LLC (1 "top research leader")
- Quattromed Cell Factory OÜ (1 "top research leader")

Most of the publications and "top research leaders" are from University of Tartu (250 publications and 100 "top research leaders") and Tallinn University of Technology (69 publications and 31 "top research leaders").

The significant presence of "top research leaders" in biotechnology research areas in the National Institute of Chemical Physics and Biophysics shows that Estonia has managed to create links between "hard sciences" i.e. chemical physics and biology, recognized at an international level.

Furthermore, it may be noted that certain biotech companies are involved as primary institutions of some "top research leaders". Considering the close relations between research institutions and biotech companies, it may be assumed that many more "top research leaders" are involved in these and other companies. This brings international scientific credibility to Estonian companies.

Level of Maturity
The analysis shows that Tallinn University of Technology is oriented more towards applied research (86% of top publications are of maturity level 3 or 4 representing 59 publications). The University of Tartu is present on both levels (166 publications of maturity level 3 or 4 representing 66%).

Internationally recognized scientists on applied research (maturity level 4) have published in the following fields, in decreasing order of number of publications:

In University of Tartu:
- Bioinformatics & Genetics (20)
- Genetics & Drug discovery & Diagnostics – Human (7)
- Drug discovery (4)
- Instrumentation & Research protocols (3)
- Bioinformatics & Drug discovery (2)
- Environmental diagnostics (2)
- Applied pharmacology (1)
- Gene engineering technologies – Plants (1)

In Tallinn University of Technology:
- Bioprocessing (4)
- Applied pharmacology (3)
- Instrumentation & Research protocols (1)
- Drug discovery (1)

In Estonian Biocenter
- Applied pharmacology (1)
- Genetics & Drug discovery & Diagnostics (1)

National Institute of Chemical Physics and Biophysics
- Environmental diagnostics (4)

Tallinn University
- Instrumentation & Research protocols (2)

Quattromed Cell Factory OÜ
- Environmental diagnostics (1)

All institutions together, the most represented research fields closest to market are:
- Bioinformatics & Genetics (20)
- Genetics & Drug discovery & Diagnostics (8)
- Environmental diagnostics (7)
- Instrumentation & Research protocols (6)

Precise applied research existing in the various business fields has been studied in each business field (cf:*2. Technology transfer of modern biotechnology*).

Research Topics with the Most Internationally Recognized Research Competences
The following table presents the business fields for which the high-quality research in Estonia has most potential for application.

Table 5: TOP research applicable under different Business Fields

Potential application domain – Business field	*Total number of publications*	*Maturity level*	*No of publications per maturity level*	*No of people per maturity level*
Therapeutics	136	2	4	2
		3	124	56
		4	8	6
Diagnostics	104	2	4	2
		3	96	45
		4	4	3
Environmental monitoring & Bioremediation	44	3	37	15
		4	7	4
Plant breeding	32	2	25	6
		3	6	5
		4	1	1
Drug delivery	24	3	24	10
Drug discovery	18	3	9	4
		4	9	7
Bioprocessing	12	3	8	3
		4	4	3
Biomass degradation	3	3	3	2

Internationally recognized high quality research in Estonia has applications mainly in the following business fields: Therapeutics and Diagnostics and, to a smaller extent, Environmental monitoring and Bioremediation, Plant breeding and Drug delivery.

According to the analysis, the business fields with the most published level 4 maturity research are, in decreasing order: Drug discovery, Therapeutics, Environmental monitoring, Diagnostics, Bioprocessing and Plant breeding.

The following table presents the therapeutic or Life Sciences areas in which internationally recognized research has occurred.

Table 6: TOP therapeutic or Life Sciences areas according to their maturity levels

Potential application domain – Business field	*Total number of publications*	*Maturity level*	*No of publications per maturity level*	*No of people per maturity level*
Neurosciences	44	3	43	17
		4	1	1
Environment	42	3	35	14
		4	7	4
Cancer	38	3	32	14
		4	6	5
Autoimmune disorders & inflammation	34	3	34	14

Potential application domain – Business field	*Total number of publications*	*Maturity level*	*No of publications per maturity level*	*No of people per maturity level*
Infectious	17	2	7	1
		3	10	7
Cardio-vascular	16	3	14	6
		4	2	1
Reproductive medicine	12	2	1	1
		3	11	5
Phytobiology	10	3	9	7
		4	1	1
Instrumentation & Research protocols	4	3	4	3
Developmental biology	2	3	2	1
Gene engineering technologies	2	3	2	2
Dermatology	1	3	1	1

Neurosciences, Environment, Cancer, Autoimmune disorders & inflammation, Infectious, Cardio-vascular, Reproductive medicine and Phytobiology are research areas with more than 10 publications in the internationally recognized, high-quality journals. They represent areas where high-quality research is done.

The most "natural" business fields in which research in a given therapeutic or Life Sciences area has potential for application are:

Therapeutic & Life Sciences areas	*Biotechnology business fields for potential application*
Autoimmune disorders & inflammation	Therapeutics
Cancer	
Cardio-vascular	
Dermatology	
Developmental biology	
Infectious	
Neurosciences	
Reproductive medicine	
Autoimmune disorders & inflammation	Diagnostics
Cancer	
Cardio-vascular	
Dermatology	
Developmental biology	
Infectious	
Neurosciences	
Reproductive medicine	
Environment	Environmental monitoring & bioremediation
Phytobiology	Plant breeding
Instrumentation & Research protocols	All
Gene engineering technologies	All

Examples of corresponding products and services are described in the analysis of the business fields (cf: *2. Technology transfer of modern biotechnology*).

Fundamental Research

Very fundamental research (maturity level 1 or 2) is not well represented in the previous section as it is usually transversal (applicable to a broad range of therapeutic and Life Sciences areas and business fields). However, it is the supporting base of all applicable research and must be pursued in order to guarantee innovation. Very fundamental research fields with "top research leaders" are:

		Nb of publications
Fundamental biophysics and biochemistry		15
Gene engineering technologies (including virology in this objective)		6
Genetics		11
Photosynthesis		26
Proteomics	Human	39
	Microbiology	14

These research fields have potential applications in numerous business fields and therapeutic & Life Sciences areas.

A significant number of "top researcher leaders" have published in the field of evolutionary genetics (10 researchers for 34 publications). Business applications of this research field are difficult to identify, though considerable bioinformatics is associated and knowledge generated on gene transmission could eventually lead to more functional understanding of genetic expression or functionalities.

In the same way, quality research linked to macro-observations has been published: epidemiology (3 publications) and ecology (2 publications). The knowledge generated in the corresponding therapeutic or Life Sciences area supports the general development of the field though it does not have necessarily direct applications.

Conclusion

The presence of high-quality, internationally recognized research in a field indicates a potential for generation of added-value results that can then be transferred to the market (given the required technology maturation tools are existent and efficient). Furthermore, existence of quality scientists contributes to bringing to the related business fields the international scientific credibility necessary for a competitive position in the global market.

Estonia may count most on recognized research in the areas of Neurosciences, Environment, Cancer, Autoimmune disorders & inflammation, and, to a more limited extent, Infectious, Cardio-vascular, Reproductive medicine and Phytobiology. With applications in the Therapeutics and Diagnostics business fields and, to a smaller extent, Environmental monitoring and Bioremediation, Plant breeding and Drug delivery.

According to the analysis, the business fields closest to the market are, in decreasing order: Drug discovery, Therapeutics, Environmental monitoring, Diagnostics, Bioprocessing and Plant breeding. Research fields supporting these domains are: Bioinformatics & Genetics, Genetics & Drug discovery & Diagnostics, Environmental diagnostics, Instrumentation & Research protocols.

3 Assessment of Business Models of the Estonian Biotech Enterprises

Main Business Models in Biotech

There are two extreme "business models" in the biotech sector. Biotech companies have a business model that is either Services-oriented or Products development-oriented or a mix of both, all of the different combinations being possible.

Usual services-oriented models are generally short- to mid-term models with limited investment requirements, turned towards local economic development with local employment perspectives, limited industrial property requirements and relatively low value creation & locoregional business as explained in Table 7.

Table 7: Characteristics of Product development and Service business models:

	Services-oriented model	*Products development-oriented model*
Time to market	Short to medium (depending on the intensity of the innovation and the regulatory pressure: ~1 to 3 years)	Very long (depending on the intensity of the innovation and the regulatory pressure: ~8 to 12 years)
Capital intensity	Less important, less risks and faster access to markets – but difficulties to attract Working Capitalists (VCs) with such business models, as Returns on Investments (ROIs) are typically smaller	Very important – very capitalistic with high risk and long ROI requiring important presence of specialized investors accepting such particularities (Business Angles, VCs)
Value creation	Limited	Potentially extremely high (blockbusters being > US$1bn revenue/year)
Research intensity / degree of innovation	Low to high (depending whether the service is based on an innovative technology or if it is based on existing technologies). The current trend is to develop "centres of excellence" for technological services as a replacement of traditional platforms which was considered as more basic technology	High to very high
Size of the company	Medium (usually 20-50 people including a large proportion of technicians – a more important part of the staff is dedicated to support functions: customer relationships, logistics, billing etc. and, in extreme cases R&D staff can be limited or inexistent)	Small (very seldom more than 20 people with a large proportion of highly qualified people – very large proportion of people working in pure R&D)
Potential exit strategies for investors	Continuous revenues from service Acquisition	Out-licensing of product to a large industrial partner Product launch (very rare except for niche markets) Acquisition by a large industrial partner Initial public offerings (IPO)
Regulatory pressure	Generally less important (except for partners subject to GCP, GMP or GLP conditions such as CMOs)	Very strong (very strict & long marketing authorizations procedure)
Importance of Industrial Property	Not necessary, required however more and more privileged	Highly important (for a long time the companies' assets and value consist of its Intellectual Property (IP)) Strong patent portfolio and IP strategy is key
Countries and markets	Local and regional aspects are key due to the necessary proximity with customers (Baltic countries, Eastern European countries, Russia, Scandinavian countries, and other historical country relationships) Western Europe and north America would only be interested with really cutting edge centre of excellence or very low price services (however Chinese or Indian competition is very hard in this respect)	Western European countries (more UK than Germany or France), North America (USA, CA), Japan Countries that have already adopted the knowledge base economy system for a long time Markets are internationals due to international unmet needs, however USA, Europe, Japan, Brazil, and now India & China are the most important

Development-oriented product models are mainly mid- to long-term models with important investment right from the beginning when the business is not yet sustainable rely strongly on patent portfolio and lead to high value creation and worldwide business as stated in Table 7.

Where does Estonia stand in terms of business models?
Most of the biotechnology companies in the new EU Member States operate as services firms with a large portion performing contract research organizations (CROs) and manufacturers (CMOs)[86]. According to Europabio report that examines biotechnology sector in new EU member states (including Estonia) and candidate countries, around 70% of the biotech companies in the 14 countries operate as services firms with a large portion performing contract research and manufacturing. One enterprise out of 30 biotech companies investigated in Estonia operates in the field of therapeutics, 26 in the field of Biotechnology/ research and development services and 1 company in another field[87], the turnover form Estonian biotech companies in 2003 came from the sales of products and half of it from services[88], although Talpsep[89] states that the company with largest turnover got 80% from its turnover from brokerage.

It was estimated at an interview that 70% of Estonian companies are in Universities, mostly operating with means from Enterprise Estonia. These companies are mostly operating out of a mission and not so much for money. Lack of money in these companies also means that the development is hindered. Another 10% of the companies' trade to fund product development, 10% sells services for that and 10% have attracted foreign investments. In past few years the number of companies in last two categories has shown a growing trend according to the interview.

In the following section Estonian biotech sector is viewed from different characteristics of products development and services business models.

Time to Market
Time to market in Estonian Biotech companies is in average rather short due to the status of the financing system. Most of models are based upon a mix of development and commercialization of services aiming at contributing to the financial support of internal research and development project development that may lead to product development and launch. Most of the system is then oriented towards development and commercialization of services.

Capital Intensity
Estonian biotech sector can be characterized by realization based financing scheme, which means that companies' main financial resources come from selling their products and services. Contrary to the Estonian scheme, in Europe main financial resources for companies in start-up phase are love money, business angels, seed capital funds and venture capital funds. Another financing system has emerged in Western countries due to the limited level of investment of the venture capital in the biotech world as well as the absolute need for innovation in big companies. It is based on early collaboration, deals and alliances with bigger or big companies once the proper proof of concept demonstration and the really secured industrial property status of the project have been performed. This system requires a highly professional early development under the standard of the industry. This is the preferred solution to avoid dilution and loss of control over the structure. In Estonia only a few companies have been funded by venture capital[90].

From the aspect of capital intensity, Estonian biotech sector tends to have the characteristics of a service based model.

Value Creation
The average sales turnover of Estonian biotech companies is lower than in other European countries with more developed biotech sector[91]. In 2007 the largest revenue of a biotech company in Estonia was 73,875,547 EEK and the highest net profit was 22,943,577 EEK. The average revenue of a biotech company in 2007 was ca 13 million EEK, net profit 1.5 million EEK[92]. There has been a growth both in terms of revenue and net profit. In 2003 average revenue of Estonian biotech company was 4,1 million EEK and net profit 0,3 million EEK[93].

86 *Biotech in the New EU Member States: An Emerging Sector,* Europabio & Venture Valuation, 2009; *Eesti Biotehnoloogia kuludepõhine innovatsioonimudel.* Kask, I, Tartu Ülikool, 2005*; Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005
87 *Biotech in the New EU Member States: An Emerging Sector*, Europabio & Venture Valuation, 2009
88 *Eesti Biotehnoloogia kuludepõhine innovatsioonimudel.* Kask, I, Tartu Ülikool, 2005
89 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005
90 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid*. Talpsep, T, Tartu Ülikool 2005, *Eesti Biotehnoloogia kuludepõhine innovatsioonimudel*. Kask, I, Tartu Ülikool, 2005
91 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005
92 EY-s calculations based on data available at agent.aripaev.ee; Calculations are based on a sample of 41 enterprises
93 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005

There has been a growth of Estonian biotechnology sector, but the revenue and net profit figures are still relatively small and characterize rather services based business model.

Research Intensity / Degree of Innovation

The current study has shown that the level of research in Estonia is rather advanced. There are a number of cutting-edge researches, but innovation is not properly valorised. Interviews showed that Estonia lacks a bridge between academy and industry transforming high-tech solutions to applied research.

Size of the Company

77% of Estonian biotech companies had less than 10 employees in 2003[94]. In 2007 this percentage had decreased down to 59%[95]. According to Europabio report[96], around 40% of employees in the Estonian biotech sector are research and development and 60% non-research and development employees. This ratio demonstrates that Estonia is on the way to the knowledge-based economy but still has to increase its ration of research and development vs non-research and development employees.

Potential Exit Strategies for Investors

The interviews conducted by Talpsep showed that in 2005 most biotech companies had not thought of an exit strategy for their company. Some of the companies had thought of selling the company as an exit strategy.[97] According to interviews done during this project, the only current exit is the licensing-out of a very limited number of projects leading to limited alternatives for investors.

Regulatory Pressure

According to interviews conducted during the study, regulatory pressure is increasing both at drug development and novel food levels leading to increasing costs of development and often longer terms.

Importance of Industrial Property

The survey in 2005 showed that there are very few companies interested in patenting[98], lack of money and interest were often mentioned as reasons for not patenting. By now the number of patents has increased, but still interviews conducted by EY showed relatively low knowledge and skills in patent writing, filing and prosecution limiting the potential of patent application of researchers from universities and institutions. Technology transfer of industrial property (licensing-out) from academia to the private industry in also very limited due to the poor number of business development managers.

Countries and Markets

Estonian biotech sector exported around 60% of the products and services in 2007. In 2003 the number was somewhat smaller. The export markets are mostly Estonia's neighbouring countries, but often also United States and there is a case of exporting to Japan and Taiwan, which shows the product development orientation for some companies, but refers rather to the service based business model[99].

Most of the aspects analyzed above show that Estonian Biotech companies operate more according to the service business model.

What evolutions in Business models?

Recently there have been changes in economic and social context:

Economic environment

There has been a major economic crisis that will lead to long and acute recession periods for many countries:

The most significant news-making event of the year was the turmoil in the capital markets:

- Biotech financing fell by 46% to US$16 billion
- This impact mostly occurred in the public markets. VC funding held up relatively well (but VCs have become more selective).

94 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005
95 EY-s calculations based on data availible at agent.aripaev.ee, Calculations are based on a sample of 41 enterprises
96 Europabio & Venture Valuation (2009). Biotech in the New EU Member States: An Emerging Sector.
97 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005
98 *Eesti biotehnoloogiaettevõtete strateegilised arhetüübid.* Talpsep, T, Tartu Ülikool 2005
99 Based on data available at agent.aripaev.ee, sample of 41 biotech enterprises

But the global financial crisis has also widened the gap between haves and have-nots:

- Across the globe, financial success was driven mostly by a few mature companies.
- The large pool of have-nots, however, have had to scramble to restructure operations, lay off workers, seek alternative sources of capital, focus pipelines and partner to survive.

- Valuations plummet
- Financing fell sharply
- Haves and have-nots

- Markets down, companies trading below cash
- Funding down 46%
- Large numbers with <1 year cash
- Restructurings up

However, despite the financial crisis, financial performance remained relatively solid:

- Revenues of publicly traded companies grew by 12% – a little below growth rates in recent years, but still in solid double-digit territory
- Global net loss improved by 53%, and the US publicly traded industry reached aggregate profitability for the first time in history
- Deal making remains brisk. In US, the potential value of alliances set a new record, and the value of M&As reached the new high (adjusted for megadeals in prior years). Key drivers -- pharma's reinvention and financial crisis -- will continue to fuel deals in the months and years ahead.

- Double-digit revenue growth
- Net loss improves
- Deal activity remains strong

- Revenue grows 12% to US$90b
- Net loss falls 53%
- US reaches aggregate profitability
- New deal highs in US market

In addition, there have been changes in the way big countries see Life Sciences: a shift from treatment to prevention, brands to generics.

Social Environment

There is a growing consumer understanding of the impacts Life Sciences products can have on their well-being as well as position by taking on proposed products and services (GMOs, organic products etc).

Changes in economical and social context have led to changes for the companies:

For big companies, the challenge remains the low productivity of R&D activity as well as the remaining low flexibility of structures

Within small companies, the difficulties to raise money resulted in the reorientation towards new sources of financing as well as flexibility with their initial business models, difficult to follow in a world changed by the economic crisis.

To understand the impact that the crisis is having on the industry's business model, it is important to understand the model itself.

- The biotech business model, like all business models, did not emerge in a vacuum. Rather, it was shaped by the constraints and necessities facing investors (who provide the model's key input: funding) and companies (who produce the model's key output: innovation).
- For instance, companies face one inescapable necessity: it takes US$1-2 billion and over a decade for a biotech company to go from startup to being sustainably profitable. And since investors face their own constraints around access to capital and funding horizons, this has led to a business model that we characterize as "the world's longest relay race". Investors and partners invest for a few years before "passing the baton" to the next investor.
- Given fickle investor sentiment, companies try to strike a balance between raising capital when funding is available and doing so at valuations and terms that do not overly dilute existing investors. This necessity leads firms to run lean operations and raise just enough capital to get to the next value-creating milestone.
- Lastly, because smaller companies have historically had less bargaining power than larger firms, the returns from out-licensing a product are typically lower than those a firm could realize from commercializing the product itself. As a result, the ultimate goal of most biotech companies that do not get acquired is to become a fully integrated pharmaceutical company. Companies may out-license their first product to bring in a revenue stream, but they seek to bring subsequent products to market themselves – a phenomenon that is often referred to as "selling your first born in order to bring your second born to market yourself."

The different Life Sciences domains are undergoing a continuous evolution of their business models, recently accelerated by the global economic context. Business models in biotechnology have started to move from total integration mode to virtual integration mode and from virtual integration to rather total virtualization modes.

Table 8: Evolution towards more virtualization mode

Modus operandi (2000-2020)

	Total integration mode *Everything is done by the company* *2000*	*Virtual integration model* ***Outsourcing*** *Partnerships / sub-contractors* *2008*	*Total virtualization mode* *Networks of excellence* *2015*
Sales and distribution	X	CSO: contract sales organization	Internal key functions: Project management and knowledge of the products, very advanced technological and regulatory competences to be able to correctly manage the partners of the network of excellence
Production	X	CMO: contract manufacturing organization	
Regulatory support	X	CROs: contract research organizations	
Development	X	CROs: contract research organizations	
Research	X	Academics, researchers, institutions	

Moving from total integration mode towards total virtualization mode brings along a number of changes. Total integration mode needed large structures for operating as most of the core functions were fulfilled by the company, which meant difficulties for small companies and countries to compete. Virtual integration or the outsourcing mode divided the functions up from the point of view of proximity, low price and/or trustworthiness, which as recent developments in biotech sector have shown gives advantages to countries which can perform at a low price. Moving further on to the total virtualization phase brings opportunities for small structures with advanced technological and regulatory excellence competences as part of a global and international network. The evolution of characteristics moving from one mode to another is outlined in the following table:

Table 9: Characteristics of business models

	Total integration *Everything is done by the company*	*Virtual integration/* *Outsourcing* *Partnerships / sub-contractors*	*Total virtualization* *Networks of excellence*
Clients	Consumer clients / real needs little analyzed and not in depth / creation of the needs by the actors on the market	>>>>>>	Very informed clients controlling their consumption / progressive evolution towards a model integrating client expectations
Product mix	Products	Products	Solution: products & high-tech services
Marketing	Traditional marketing	>>>>>>	Multi-canal marketing (e-marketing)
Sales force	Numerous >>>> less numerous >>>> limited number of very advanced competences & knowledge		
Biotech innovation financing	Personal investment / stock-market integration	Partnerships and VCs: most important financing sources / foundations	VCs, foundations, Big industrials become financing partners given the correct POC is achieved
Organization flexibility	Very rigid	Flexibilization of the structure and the operation	Very flexible
Economic model	A unique traditional model	>>>>>>	Several evolving models coexisting
Growth	Internal growth	External growth / merger and acquisitions	External growth / merger and acquisitions
Targeted markets	Developed markets >>>>>> Emerging and developed markets		
Globalization	Think globally, act «westernly >> Detect locally, think globally (knowledge based-economy), act locally		
Outsourcing	Control on the whole chain	R&D done by biotech companies	Everything is outsourced / creation of small research structures
		Market access and distribution provided by pharmas	Internally: advanced knowledge in the domains concerned and competences in project management
Partnerships/ network	A limited number of partners, mainly in connected functions (distribution, packaging)	Externalization of R&D to biotech companies	System based on a network of partners/network of excellence for the whole value chain. Networks of transversal partners (different sectors: agrofood, nutraceutics, etc – different competences: biology, IT, etc)
Patents / IP	Large patents enabling an umbrella protection of innovation	>>>>>>	Very targeted patents, positioned on large "niches"
Costs	Not optimized	First optimization of costs due to the variabilization of previously fixed costs	Optimized costs
Regulations	Heavy >>> more and more heavy		
Risks	Very high risk due to specialization	Better controlled risks	Mutualisation of risks through the networks of partners

According to Datamonitor's report[100] the trend towards virtual integration has become more and more visible in the world, with big companies restructuring themselves. This new evolution may be considered in two ways: either horizontally through autonomous networks of excellence per stage of development (e.g. Eli Lilly early phase drug development group) or vertically (networks of excellence per therapeutic focus, e.g. GSK and its 6 therapy specific Centers of Excellence for Drug Discovery or Novartis with oncology), allowing companies to move away from the old "fully integrated" research and development operating model, into a more agile organization. It enables focusing on key elements of value chain, reducing risk, spinning out business units; reducing complexity of an organization; introducing greater strategic and financial flexibility. GlaxoSmithKline provides an example of horizontal restructuring, while Eli Lilly illustrates vertical disintegration of the value chain.

100 *New Approaches to Pharma R&D. Evolving strategies to rejuvenate R&D efficiency,* Datamonitor 05/2009

- In 2002-2003 Eli Lilly created an autonomous early phase drug development group operating on a fully outsourced model to advance drug candidates from discovery to proof of concept. The aim was to increase cost-effectiveness of R&D and speed up the drug development process by using external CROs for specific areas of drug development. This model has increased productivity, with drug development reaching proof of concept in 29 months as compared to Eli Lilly's average of 40 months, at a cost of US$3.2 million instead of Eli Lilly's US$15 million). Further illustrating Eli Lilly's confidence in the model, Eli Lilly set up an equal joint venture in October 2008 with one of India's leading CROs – Jubilant Organosys. This partnership, named Vanthys, is also based on the same model, illustrating a trend towards a more virtual model.
- After the merger between Glaxo Wellcome and SmithKline Beecham in 2001 GlaxoSmithKline created Centres of Excellence for Drug Discovery (CEDDs) for six therapy areas, in a move designed to incentivize bringing compounds to proof-of-concept stage as fast as possible. As measured by the number of proof of concepts delivered, these autonomous groups increased the company's productivity, however, the commercial potential remains questionable. The CEDD model has since been upgraded, adding a Centre of Excellence in External Drug Discovery (CEEDD), which focuses on in licensing and collaborative projects, however, securing successful late-stage deals has proved challenging.

This shift is particularly important as it gives the opportunity to small entities to be referenced in a network as a centre of excellence in a particular subject at international level.

Estonia in terms of Business model evolution?

There are examples of first two business models in Estonia with a growing trend towards willingness to become part of the worldwide network of excellence.

For example companies like Asper Biotech operate mainly according to total integration model and most of smaller companies according to virtual integration model. Estonian companies are mostly too small to operate according to total integration model and virtual integration model might not prove to be very viable because of the volume and price pressure from India and China. Small niche research groups on the other hand allow applying advanced research as a part of networks of excellence, which could be the way for Estonia. There are already a few structures (competence centres) which can serve as platforms for such networks, there is also a high level of internet usage and applications which is also crucial for total virtualization phase.

Suggestions

The development of a biotechnology business sector in Estonia would require:

- coming from services business model and with time turning into a mix of products development and high-tech services business models with the aim of belonging to international network of excellence;
- to focus on drug and biomarkers discovery through the use of enabling technologies such as bioinformatics, genetics & pharmacogenomics in order to consolidate diagnostics development for health, nutrition and environment with a strong clinical & translational research field for long-term drug development & manufacturing;
- to contribute to the creation of scientific and managerial know-how in the health/nutrition/environmental sectors and results in the creation of employment and new economic opportunities. It also promotes the establishment of research and development and SME support infrastructures which benefit more advanced research and development,
- to secure knowledge based economy through strong support of voluntary industrial/intellectual property policy.

Thus, Estonia should keep strengthening the service based biotech industry, but at the same time promote aspects that help to push Estonia more towards the product development model. Estonia should use the new trend towards more and more virtualization to built a couple of focused "centres of excellence" with the objective to make these centres visible at international levels for their outstanding research and quality and built around them the ad hoc network that will contribute to producing shared or fully owned industrial property for licensing-out and economic returns.

4 Policy Recommendations for the Estonian Biotechnology Program

4.1 Key Success Factors

The evolution of research into industrial application acquires four main steps: Fundamental research, Innovation in particular research field, Applied Research and Conditions for industrial applications.

Fundamental research	Innovation in particular research field	Applied Research and early development	Industrial development and launch
■ Publications in high impact factors ■ International scientific research workforce (PhD & MD) ■ Top Research Leaders (TRL) ■ Quality of scientific results	■ Patent anteriority study ■ First patent application to initiate patent portfolio ■ Publications in high impact factors ■ Publications in field specific journals focused on applied research ■ Key Opinion Leaders (PhD, MD) ■ Quality and cutting edge innovation ■ Preliminary proof of concept ■ Market assessment for innovation positioning and preliminary feasibility of the innovation	■ Enthusiastic, completed and motivated team in case of valorization through start up creation ■ Key Opinion Leaders (PhD, MD) support ■ Consolidated patent portfolio ■ Freedom to operate ■ Full proof of concept compatible with industrial standards ■ Comprehensive market assessment ■ Multi-axes development plan (technology, industrial property, freedom to operate, business development, human resources, production scale up, regulatory.) ■ Licensing out or company creation	■ Licensing in ■ Manufacturing ■ Late development and validation ■ Regulatory ■ Product/services launch

Figure 28: Four main steps of the evolution of research industrial application

The analysis of the biotech business fields has shown that there is a clear gap in Estonia between fundamental research and the first identification of an innovation and its development by the industry. The reinforcement of applied research and early development phase is a key element to reduce the gap between innovation in research and development under industrial standards.

Case Studies to Identify Solutions and Best Practices to Reduce the Gap:

Maturation tools:

- **Canadian example of maturation system: Genome Quebec**

  A private organization funded by public and private structures working under the standards of the international biotech research industry to drive project from fundamental academic research towards applied research and development with secure industrial property status and industrial proof of concept ready for licensing out. This is achieved by a senior workforce of technology developers, regulatory people, business development and marketing people with pharmaceutical industry processes in particular with respect to project's selection, project management (ability to kill projects), alliance and outsourcing management, out licensing activities).

- French example of maturation system: Genopole

  Genopole is aiming at combining local economic development with excellence in biotech by developing centres of excellence accessible to the whole biotech/pharma/diagnostic/food industries and working under the standard of the industry (quality control, quality insurance, and respect of timelines, confidentiality of the data and studies, reproducibility, senior workforce). Genopole has structures several high tech services platforms, so-called centres of excellence in particular areas (biomanufacturing, shared lab animal house, small animal bioimaging platform, gene therapy manufacturing plant). Genopole's strategy is to conciliate high technology product-innovation industry in life sciences (high value but huge risk and long-term) with biotech services industry and academic platforms (lower value but limited risk and short to mid-term).

  French example of maturation system: French National Agency, a project-based funding Agency to advance French research

  The French National Research Agency so-called ANR, a public institution for the management of administrative issues, was created on January 01, 2007, and is a funding agency for research projects. Its aim is to increase the number of research projects issued from the entire scientific community, and to provide funding based on calls for proposals and peer review selection processes. ANR addresses both public research institutions and industries with a double mission of producing new knowledge and promoting interaction between public laboratories and industrial laboratories through the development of partnerships. Through the call for proposals (CFP), projects are selected based on their scientific quality, as well as on their economic relevance for industries, when applicable.

  The context of the creation came from insufficiently tested biotech innovations with technological inventions resulting from public research in the biotechnology sector too often insufficiently supported or too many endogenous companies created on inventions with insufficiently tested concept, explaining consequently the difficulties to find industrial and/or financial partnerships as well as the limited chances of success of such companies.

  ANR has launched in particular two calls for projects, one on emergence and maturation of projects with strong potential of valorisation (so-called «Emergence-BIO») and one dedicated to partnership research between industry and academic laboratory in biotechnologies for health (so-called «BiotecS»).
  Project selection is based on committees of international experts (scientific, clinical, business development, marketing, patent attorney or financial experts).

  Within the framework of Emergence-BIO, ANR wishes to support the complementary technological developments and studies, aiming at consolidating the proof of concept according to industry standards, the intellectual and industrial protection status, and the commercial exploitation of biotechnological inventions. The complementary technological developments and studies are supported by ANR within the range of around € 200-300,000 per project. This program is only dedicated to the academic research (not the industrial research). It has a strong link with the technology transfer structures in universities or institutions.

- Belgium example of maturation system: the technology transfer office from the VIB

  A global and unique technology transfer office with biotech dedicated workforce working in close, long-term and trusted relationships with several universities. VIB takes part in the financing of the proof of concept and overall in the financing of the research and development phase (not easily acceptable by the banks without compensation) allowing a lever effect for companies, a limitation of "damp squibs" (insufficiently tested innovations), resulting in growth of innovations. Meanwhile this allows to define the sectors of excellence of the country in order to avoid scattering and too general positioning, the research themes within each strategic segment, and to develop and make accessible to the private and public actors necessary tools and means for the maturation of technology: research centres, specific service offers.

  This initiative federates all of the actors of the innovation sphere including companies, universities, valorisation structures, government agencies. The gathering of these actors, private and public, and the mutualisation of their means are necessary to the development of technology maturation. An example of gathering opportunities can be a common and crossed work on national scale projects transformation of laboratory projects into company projects (industrial partnership, company creation).

This type of structure has to be very strict in the selection of the projects to finance: solidity of the business plan, significant existing scientific results, and industrial property protection status. There is a need to confirm that each project has sufficient valorisation potential (economic impacts). One solution is to rely on existing structures (valorisation structures) to facilitate the organization and the selection of the projects (pre-selection) and to communicate and inform on the advances Biotechnology research in order to develop a thought leadership and a position as major player at both national and international levels.

Financing tools:

- **French example of seed funding:**

INSERM Transfer initiative: a seed and pre-seed investment for valorisation of projects from public research

INSERM Transfert Initiative is the Venture Capital fund of INSERM, the French national public research institution entirely devoted to biological, medical and public health research. IINSERM Transfert Initiative is focused on seed and pre-seed investment in the life/health sciences field. The initiative was created by INSERM and 3 financial partners. It is associated with four major actors for the financing of biotech start-ups: CDC Enterprises, a major institutional investor, Sofinnova Partners & Ventech, two life sciences dedicated venture capital, and Inserm Transfert SA, the technology transfer office of INSERM.

It has been created in 2002 and has invested 800,000 in 11 companies, with a 4,2 million fund and average investment ranking between 100 à 300,000 by project.

Targeted biomedical specialties are therapeutic agents, tools and technological platforms, diagnostic tools and medico-surgical material.

Under the course of its activity, selection process is a key element: the quality of existing scientific results, an enthusiastic and motivated team, a strong industrial property portfolio, clear commercial opportunities and realistic strategy and business model.

Key Success Factors:

- Ability to take the decision to focus on certain business fields in terms of national support
- Availability of patent filing & prosecution skills (patent filing, prosecution, litigation) dedicated to biotechnology subjects at both academic and industry level with international experience
- Availability of business development & marketing skills dedicated to industry business fields (food, energy, environment, health) for both technology transfer offices from universities and institutions and companies
- Dedicated technology transfer centres in universities and institutions at international standards (see VIB case study)
- Innovation maturation support organization or structure to fulfil the gap between research innovation and applied development (see Genome Quebec case study or Genopole case study) through selection of projects to integrate, maturation and development of projects according to industrial proof of concept standards, out-licensing of newly developed project to the industry
- Awareness of the strategic positioning of industrial/intellectual property
- International research workforce
- Ability to publish in journals with high impact factors including for clinical research subjects
- National authority capacity to select business industry fields' projects or academic research project according to a focus and clear strategy aiming at concentrating support on the most promising business fields
- Dedicated specialized seed funding (with good understanding of correlated timelines and ROI) to support the gap
- Change from solely services business model towards mix services and product-oriented business model with major efforts on products.
- Build focused internationally recognized centre of excellence entities aiming at entering international networks of excellence

4.2 Main Risks

- Failure in implementing any biotech industry
- Loss of the remaining research people and national research potential located in Estonia.
- Failure to build knowledge-based economy system in Estonia.
- Limitation of the scope of current industry fields to traditional industries (healthcare, food industry, environment-related industry, energy industry, forestry industry)
- Loss of market share by the traditional industries at both national and international levels.
- Bankruptcy of certain companies within traditional industries (healthcare, food industry, environment-related industry, energy industry, forestry industry) in the long–term.

4.3 Action Plan

- Suggestions based on identified Estonian key success factors and international best practices to reduce the gap, between research innovation and applied development, and build a sustainable ecosystem:

  Structure a financing chain for the companies' complete life cycle. There is a need for the creation of a global investment system for innovating companies covering all stages with:
  - Incentives & grants
  - Advances and loans (banks, state)
  - Equities (BA, VC's)
  - Guarantees

  The objective is to identify all the financing possibilities offered to innovating companies in biotechnology (and under which conditions) and make sure there is coherence between the various tools (i.e. that there are no gaps or missing links, but also that there are no duplications).

  As Estonian financers cannot offer the whole financing chain, the possibilities offered by Estonia's neighbours should be considered (Scanbalt, Medicon Valley, Finland, etc). The objective for Estonia is to identify what is not present and/or available in this Scandinavian & Baltic financing landscape for Estonian companies and develop measures to address these gaps. It is all the more important that the early development steps are properly covered as the largest gaps identified are there.

  Differences between Food & Healthcare business fields: The healthcare business fields require, in general, larger amounts of financial investments (due to high regulatory constraints). In the food industry, development of innovation usually requires less time and smaller amounts of money so industries can cover a larger part in the financing chain. This can be observed, for example, in the role of the industrial investments in the competence centres and the greater readiness-level of the projects thus financed. Therefore, gaps are most important for the healthcare business fields. However, the financing chain for innovation development for the food-related business fields should also be studied. Furthermore, it must be anticipated that costs will rise in functional food with developing regulations and need for more clinical validations, and gaps may appear.

- Set up tax incentives encouraging investment into innovating companies (example in France: the TEPA law makes it possible for ISF (Tax on patrimony) taxpayers to deduct 75% of their investment in SME's from their tax declaration).

- Develop dedicated specialization of financing structures such as seed funding specialized structure (see INSERM Transfer Initiative case study).

- Give support to Baltic or Scandinavian Business Angels networks for structuring and professionalization.

  It seems difficult to rely only on Estonian Business Angels, and it is therefore necessary to involve Business Angels of neighbouring countries. For this, they should be made aware of the existing high-tech Estonian technologies and research projects, for example by having the representatives of their structures visiting Estonia on a regular basis (twice a year for instance) and by better communication about the technologies in development in Estonia. Estonian government's action could include laboratory visits, presentation and discussions with existing industries and other awareness rising activities. The objective is to give awareness of where Estonia wants to go, what Estonia is excellent at, which are the success stories etc.

NB: As Medicon Valley has Nutrition and Healthcare sectors among its priority topics, it should help to attract this region's attention.

- Develop loans made with no guarantee of repayment and other public incentives allowing innovating companies to start their activity without contribution in capital (lever effect with other financing devices).

  The proof of concept stage is a bottleneck in Estonia as well as in all countries and therefore there is a need for dedicated grants and other measures to support this stage. Proof of concept is an early stage of the innovation development cycle, and therefore it is a very risky stage, with little pay-back and no guarantee of repayment. This is why financing gaps exist and they must be solved through public financing. In other countries, different measures have been developed: i.e. loans paid back only in case of success, financial investment in the capital of the company.

  To support the gap in Estonia, the following actions could be undertaken: develop loans made with no guarantee of repayment, or design other public incentives allowing innovating companies to start their activity without requiring a contribution in capital. This will also enable to have a lever effect for other financing solutions.

- Set up an accompaniment in management and economic development for entrepreneurs (seems a necessary contribution to the sustainable growth of innovating companies).

  There is a need to train managers specifically for the biotechnology sector (there are particular competences to acquire). A short-term solution is to have Estonian managers who have worked in biotech companies abroad (and thus have been trained) to return. On a longer term, a new generation of managers has to be built through training on market subjects, industrial property and freedom to operate aspects.

- Valorise technologies stemming from public research in company projects through the creation of ad hoc structures (valorisation structures or technology transfer structure).

  These structures are important to help technologies to mature more and more, and to make them transfer from universities to companies. This involves identifying excellent projects within universities, what should be patented, what is the right proof of concept for an internationally recognized out-licensing, what are the necessary business development actions to perform (business development plan) etc. The key is to have in the University the whole range of competencies:
  - Patent skills (what, how and when to patent?)
  - Marketing skills (for one technology: what will be the market?)
  - Development skills (what are the necessary steps to establish the proof of concept? (in order to avoid doing too much and/or the unnecessary scientific and technical demonstrations))
  - Business development skills (have people used to the food or healthcare industries, very well introduced in the national and international specific network (personal contact list of the right R&D or in-licensing people in the big companies or within the universities) and with track record of negotiations, business discussions and sales.

  The best possible case would be to have people who have experience in the biotechnology industry. Another key success factor is that these people should be in close relationship with companies (Estonian and foreign, start-ups to large industrial groups).

  Estonia doesn't need such multiple structures, but should concentrate efforts in having the smallest number (politically reasonable) of structure with the highest level of competences and required skills.

  Examples from successful ad hoc structure can be drawn from USA (tech transfer offices), Belgium (VIB-group of fully dedicated people), Sweden (Karolinska Institute – people not only there to sell, but with the full range of above-mentioned competences).

- Develop specific degree courses for patents, trademarks and industrial design such as CEIPI (Centre for International Intellectual Property Studies) accelerated courses dedicated particularly to scientific and technical people or encourage people to perform such additional courses on a global international environment.

  These courses should be specific to biotechnology and addressed not only to companies but also university researchers.

- Develop alliance with international MBAs degree courses with particular focus on business development activities or licensing degree courses.

- Create a life sciences Council with two major axes ("Medical Council" and "Nutrition & Food Council") interacting closely to set up the strategy at scientific level and select projects and fields to support (such as French National Agency case study) under the framework of call for tender for instance.

  The Council could be created with two boards ("Medical Council Board" and "Nutrition & Food Council Board") including scientists, clinicians, industrials from the concerned sector and business developers that consider projects in a very detailed way to select the most promising ones. The Boards should also have the mission to identify what are the key research areas. These boards may include foreign experts to avoid compromise, ensure independence and bring fresh air.

- A particular call for tender could be set up to address the special issue of in-licensing international opportunities for Estonian industries.

  The call would encourage foreign industries and research teams to propose technologies for in-licensing by Estonian industries through co-financing with the government to improve a defined process/product. This would help Estonia to have an overview of the tech transfer opportunities for its specific needs.

  Public Private Partnerships have used this system, for example to identify and select research projects to in-license.

  In a longer term, a call for tender could be set up in the direction of the Estonian industries to support the acquisition of new technologies that would be identified by the Estonian companies themselves.

- Improve transportation with international destinations in order to consolidate the capacity of Estonia to set and manage alliances properly on the long term.

  Biotechnologies are an economic sector that is developed and finds a market at a global level. Collaborations and interactions at that level are the key and therefore the easiness of international communication is central. Direct flights to, at least, large European hubs are critical for Estonia to set and manage alliances properly on the long term.

- Establish structuring equipment such as GMP facility accessible to the industry and not only academia

  Production facilities with "Good manufacturing practices" (GMP) certification are necessary to produce candidate drugs for clinical trials. Therefore, access to these facilities is a necessary step in the development process and pre-industrial and industrial scale GMP facilities are not available in Estonia. There are two solutions to give this access to Estonian companies: build partnerships with foreign facilities to help Estonian companies to have access to these (at a lower price?) or build your own facilities. This must be analyzed closely considering the number of molecules that need to be produced in GMP standards.

  Other structuring facilities, such as very large scientific infrastructure, are also a key factor. Interviews show that academic institutions have been well equipped with equipments. However, the conditions of access to these large equipments need to be clearly defined, especially if they are unique in Estonia in order to ensure they are available to R&D projects requiring them from the university as well as from the private sector (a fee for service system can be imagined).

- Develop a structure dedicated to the selection of research innovation to convert this early innovation into applied development at international industry level ready for out licensing to industry field (Genome Quebec case study)

  The identification and selection of early-stage projects to support and the way to accompany them are two of the most complex questions worldwide. Therefore some countries have decided to build dedicated structures to do this, be they independent from the existing public structures or not. An example can

be found in the Genome Quebec case study. In this example projects selected through a call for tender are granted a project manager to accompany their development to ensure they reach the development stage where they can be out-licensed to the industry.

Estonia would beneficiate greatly from a structure dedicated to the selection of research innovation at early stage in the objective to convert it into applied development that has reached the stage where it is ready for out-licensing to the industry (international level).

- Develop a national initiative labelling the most economically promising applied research projects from all priority fields recognized at national level and supporting these projects (according to CNCETI case study in the diagnostic business field section).

  The implementation of a "trademark" label, given for example annually after a national competition, and identifying very good Estonian projects would enable a greater readability of the Estonian Biotechnology landscape. This would facilitate and attract foreign investments.

- At academic level, privilege the hiring of international post docs or young scientific researchers through aggressive incentives and strict selection process

  The presence of high-level international researchers in Estonia academic research will enhance experience share (short-term) and future international collaborations and visibility of Estonia Biotechnology (mid- to long-term).

Most recommendations that have been developed above are transversal measures to healthcare and food & nutrition fields. Differences when they exist have been underlined (for instance specific board members and goals). The specificities between both should be managed at project appraisal levels and in particular according to the nature of the specific early development steps that are clearly different between these fields, for instance:

- Identification and in vivo validation of a signature of biomarkers as part of the proof of concept step on the healthcare side
- Genomic analysis and development of a novel strain for functional food or processed food.

Appendix 1 | Abbreviations

ABT	animal breeding technologies
AIID	auto-immune and inflammatory disorders
ANR	the French national research agency
AR	antibiotic resistance
BBC	bio based chemicals
BSE	mad cow disease
BW	biological welfare
CEDD	centres of excellence for drug discovery
CEEDD	centre of excellence in external drug discovery
CEIPI	centre for international intellectual property studies
CETP	cholesteryl ester transfer protein
CMO	contract manufacturing organizations
CNS	central nervous system
CPSC	consumer product safety commission
CV	cardiovascular
EDT	enzymatic deinking technologies
EPA	environmental protection agency
EPP	enzymes in the pulp and paper
ERIH	European reference index of the humanities
FD	food diagnostic
FDA	food and drug administration
FF	functional food
FP	food processing
FSH	follicle stimulating hormones
FTC	federal trade commission
FTE	full time employees
GEMS	genetically engineered micro-organisms
GMO	genetically modified organism
GMP	good manufacturing practices
HPP	high pressure-temperature processing
IP	intellectual property
KOL	key opinion leader
MAS	marker assisted selection
OC	quality control
PBT	plant breeding technologies
PCR	polymerase chain reaction
PEF	pulse electric fields
PhRMA	pharmaceutical research and manufacturers of America
QTL	quantitative trait loci
R&D	research and development
TNF	tumour neurosis factor
TTO	tactical technology offices
TTU	Tallinn University of Technology
UT	University of Tartu
VC	venture capital

Appendix 2 | Priority targets

Three types of priority targets have been identified:

- 4 priority business fields: functional food, food processing, diagnostics and drug discovery

  The fields identified in the study are coherent with the client's feeling:
  - Diagnostics is a strong domain technologically and a critical mass exists there;
  - In food sector there is a critical mass in the industry;
  - Drug discovery (i.e.: support technologies that help you discover new drugs and technologies) is strong because, in a general manner, drug discovery is, among the healthcare business fields, the one that can be reached fastest as this field is the closest in terms of to early R&D, requiring limited regulatory constrain, limited validation steps, limited time to market.

- 2 technology transfer priorities: enzymes in pulp & paper and bioenergy (with the objective of consolidating these national industries with better products)

  Supporting technology in-licensing in paper and pulp industry (enzymes) makes sense.

  In Bioenergy, the competition is incredibly complex, and it will be extremely difficult for Estonia to have a significant position in the bioenergy global market (especially considering the enormous amount of money the US government has injected in this domain). However, technology transfer for a particular bioenergy technology can be considered with the only objective for Estonia to be autonomous at the national level or the Baltic states level (joined in-licensing opportunity can be considered by Baltic states or other group of nations in order to reduce the cost of acquisition of such license). This in-licensing campaign needs to be organized, targeted and coordinated with the set up of an in-licensing plan including landscape analysis, prioritization process based on industrial property, freedom to operate, technology complexity, implementation constrains.

- 2 supportive technologies: genetics and bioinformatics

  Existing strong supporting technologies (bioinformatics, genetics, sensors) should be supported together with priority fields.

  For example:
  - biomarkers & biosensors in diagnostics
  - genomics as part of food industry projects.

  In order to create or reinforce these links between fields (biology, physics, chemistry, informatics), a key success factor is to support multidisciplinary teams, including at project level.

  For example: include as a criteria for project selection that the selected projects for funding involve competencies from different domains and that the right balance of consortium is involved (shared budget, balanced team size, shared industrial property).

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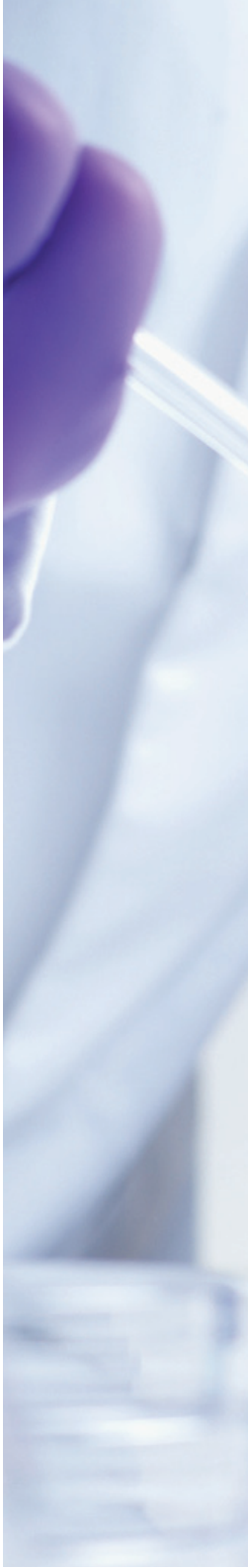

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