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A Survey of Commercial Biomolecules, Delimited to Pharmaceuticals and Medical Devices

Markus Holowacz
Annika Krans
Camilla Wallén
Alberto Martinez
Nadia Mohammadi

UPPSALA
UNIVERSITET

Teknisk- naturvetenskaplig fakultet
UTH-enheten

Besöksadress:
Ångströmlaboratoriet
Lägerhyddsvägen 1
Hus 4, Plan 0

Postadress:
Box 536
751 21 Uppsala

Telefon:
018 – 471 30 03

Telefax:
018 – 471 30 00

Hemsida:
http://www.teknat.uu.se/student

Abstract

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Biologics — biomolecule-based therapeutics — are predicted to become the next generation of therapeutical drugs. The pharmaceutical industry is investing a great amount of money into research in this medical field, which shows the importance and the need of analyses regarding biological drugs. This report is a survey of commercial biologics in which the market and trends regarding the past, present and future are analysed. The results are based on a literature study limited to commercial biologics — either as chemical entities, as conjugates to another class of biomolecules or as medical devices. The market for biomolecule-based therapeutics and medical devices is predicted to flourish as the new generations of peptides, proteins, oligonucleotides, carbohydrates and lipids increase in both approvals and sales. The fact that scientists have gained a broader comprehension on a molecular level due to advanced technologies has resulted in biologics reaching clinical maturity. The optimized pharmacokinetic properties, greater specificity, and the increased therapeutic window have led to reduced side effects compared to traditional therapeutical alternatives. Due to new development approaches — peptidomimetics — the stability of peptides has shown to increase. This results in a huge market and development potential. The protein therapeutics market is the largest among biologics, and their subgroup — the monoclonal antibody-based therapeutics market — is the fastest growing. With a high growth rate of novel therapeutics in development, the market will continue to expand. Conjugated monoclonal antibodies (ADC) and GalNAc conjugates to small interfering RNA are just a few examples of high potential drugs that are expected to increase on the market and in clinical development. Oncology is the dominating therapeutic area, where great success has been observed in both clinical and pre-clinical studies. Lipid conjugates have proven to be efficient in the treatment of tumour cells and the cytotoxic ADC grant great hope for the biomolecule-based therapeutics market. The market is also expected to grow for establishing biologics; for example the increasing need of anticoagulants is predicted to double the Heparin market to 2023 and the demand for novel treatment alternatives opens market opportunities for Heparin biosimilars. The biological vaccine market is also predicted to grow together with biologics, as mutated animal-spread diseases increase in number.

Handledare: Ulf Tedebark
Ämnesgranskare: Ulf Göransson
Examinator: Enrico Baraldi
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1. Glossary *

** The glossary is based on information from Wikipedia and Swedish Medical Products Agency (Läkemedelsverket).*

Antisense oligonucleotide – synthetic strings of DNA/RNA monomers which bind to the RNA-strain and suppresses its function

Antisense therapy – treatment for genetic disorders and infections using Antisense oligonucleotides

Apolipoprotein B-100 – A protein consisting of 4563 amino acids encoded by the APOB gene, which is synthesized in the liver. High amount of apolipoprotein B can for example result in insulin resistance

Apolipoprotein C-III – A protein produced in the liver that controls the level of triglyceride in the blood

Biosimilar – a drug very similar to an already approved biological drug, but not identical. Biosimilars has been allowed in the EU since 2006 and in the U.S. since 2010

Antithrombin III – A protease with the ability to inhibit the blood coagulation process through a non vitamin K-dependant mechanism

CAGR – The Compound Annual Growth Rate

Chronic disease – a constant or a long-lasting disease, or a disease that presents itself with time

Cushing's disease – an increased secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary

Cyclotide – are small disulfide rich peptides, isolated from plants

Cysteine – is an amino acid with a thiol group, -SH, which is able to form a disulfide bridge with another thiol group

Cytomegalovirus retinitis (CMV) – an eye infection in the retina usually caused by a herpesvirus, which may lead to blindness

Duchenne muscular dystrophy (DMD) – a progressive neuromuscular disorder resulting in muscular breakdown

EMA – European Medicines Agency

Epitope – the part of an antigen that is recognized by the immune system, specially by antibodies

FDA – U.S. Food and Drug Administration

Gene expression – transcription, RNA splicing, translation and/or post-translational modification

Hepatocyte – liver cells, responsible for the function of the liver

Heparin-induced thrombocytopenia (HIT) – is a condition associated with taking heparin drugs. The result of this induced state is unusually low levels of platelets in the blood as an outcome of the abnormal development of antibodies against heparin

In vitro – studies that are performed with microorganisms, cells, or biological molecules outside their normal biological context

In vivo – studies in which effects of various biological entities are tested on living organisms

Multiple sclerosis (MS) – the insulating covers of nerve cells in the brain and spinal cord are damaged, causing disruption in the communication of the nervous system

Pancreatitis – An inflammation in the pancreas, where the main symptoms are pain in the epigastrium (upper region of the stomach), nausea and vomiting

Pharmaceuticals – a compound manufactured for use as a medicinal drug

Protease – is any enzyme that performs proteolysis

Proteolysis – protein catabolism by hydrolysis of peptide bonds

Spinal Muscular atrophy (SMA) – a severe motor-neuron disease that is the leading genetic cause of infant mortality

Therapeutics – treatment of a disease and the use of a drug in order to treat a disease

TTR Amyloidosis – a fatal disease with a progressive buildup of an abnormal deposit, amyloid – a plaque that accumulates in organs and tissues around the body

Ulcerative Colitis – disease causing an inflammatory condition and ulcers of the rectum and colon

Watson-Crick base pairing – a purine binds with a pyrimidine by hydrogen bonds; adenine (A) binds with thymine (T) and guanine (G) with cytosine (C). In RNA thymine is substituted with uracil (U).

2. Introduction and Aim

In today's society, there is a rapidly growing market for medical treatment with biologics – biomolecule-based therapeutics. Biologics are predicted to become the next generation of pharmaceuticals and therapeutics [1]. Research in this medical field focuses mostly on biomolecules such as peptides, oligonucleotides, carbohydrates, lipids along with proteins and their subgroup monoclonal antibodies (mAbs). As the world's population gets older, with changing lifestyles and advancements in technology, higher demands are placed on the drug industry.

Therapeutics based on biomolecules have proved to be both efficient in the treatment of various types of diseases and have fewer side effects due to their higher specificity compared to traditional therapeutics. The Swedish government along with other key players are investing one billion SEK into research in this highly potential medical field [2]. This market is relatively new in comparison to other drug markets which results in lack of reports that summarize its entirety. Therefore, it is essential to invest and encourage projects in this field but also to give an insight into this new market of biologics. The aim of this project is to analyse the market of biologics.

This independent work in partnership with the state-owned institution SP Process Development (now part of RISE, Research Institutes, Sweden) and Uppsala University has a primary focus on biologics. It is an important project which summarizes the most essential aspects in this medical field. The analysis consists of clear trends that exists with regard to the past, present and possible future trends. The project is also based on annual sales and to make a survey of the most interesting biologics viewed from a global perspective and what the authors of this work find interesting. In addition, the report contains a detailed definition of the different classes of biomolecules, both in their natural state and in pharmaceutical form as biologics.

3. Methods

The results are based on a literature study limited to commercial biologics, either as separate or as conjugates to another class of biomolecules (for example mAbs conjugated to oligonucleotides), FDA/EMA approved drugs, potential drugs in the pipeline and medical devices. The literature study was based on the use of reliable databases such as Pubmed, Drugbank, ClinicalTrials.gov, and other relevant sources. The main keywords used were: *biologics, medical devices, market, trends, pipeline, the past, present, future, clinical studies, current status, research & development*. The keywords, relevant databases and articles along with guidelines regarding the report structure were established together with a technical consultant provided from Uppsala University. In order to facilitate the references with the

Vancouver system, a program named Zotero was used. This report also includes the definition of both biologics and the classes of therapeutic biomolecules along with an analysis of the market and trends — today's market globally, annual sales, the leading corporations, trends over time, pipelines, potential, research and development (R&D), eventual limitations and biosimilars. A list of the most interesting pharmaceuticals, their function/task in the human body and their therapeutic field are also included in the study. The focus of this project lies on the market and trends: in the past, the present and the future.

4. Theory

The following section defines the biomolecules covered in this report together with medical devices in order to get an overview of the relevant theory.

4.1. Biological Therapeutics

The definition of biological therapeutics according to the Swedish Medical Products Agency is as follows: *A biological drug is an active substance which is either manufactured in or alternatively have been purified from a specific material which has a biological origin* [3]. Biological pharmaceuticals are drugs with a very complicated chemical structure which is sensitive for minor changes in the synthetic route. Biologics occur in various shapes and characteristics such as vaccines, mAbs, peptides just to mention a few.

4.2. Peptides

Peptides consist of two or more amino acids linked together with peptide bonds. A peptide bond forms when the α-carboxyl group of one amino acid is joined together with the α-amino group of another amino acid, see Figure 1. The formation is an example of a condensation reaction – water is formed as a product. Two amino acids form a dipeptide; three amino acids form a tripeptide and so on. When many amino acids are joined together the product is called a polypeptide. Molecules referred to as polypeptides generally have molecular weights below 10,000 Dalton (Da) corresponding to a chain of ~100 amino acid residues[4].

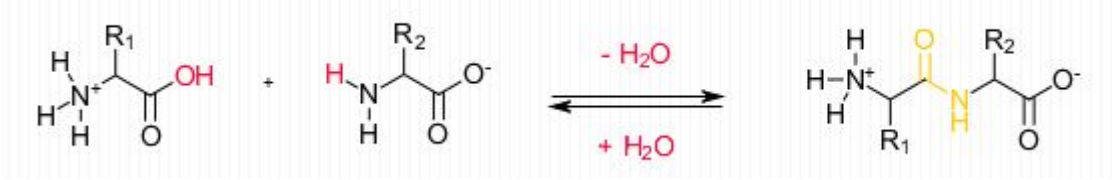

Figure 1. The figure shows the formation of a peptide bond (in yellow) when two amino acids are joined together.

4.3. Proteins

This group of biomolecules are in general referred to as very large molecules consisting of more than 50 amino acids linked together. The typical structure of a protein is the peptide bond between amino acids, and the two different terminals, the C-terminal (negatively charged) and the N-terminal (positively charged). Major classes of essential molecules including enzymes, hormones consists of proteins [5]. Proteins are essential for many biological processes in the human body. The lack of proteins will disturb the normal and correct function of our body [6].

4.3.1. Monoclonal antibodies

Monoclonal antibodies (mAbs) are identical antibodies with a unique specificity [7]. To simplify the meaning of identical antibodies, all the mAbs are produced by one sort of immune cells which means that they are clones of a single parent cell and therefore identical. Monoclonal antibodies have the ability to recognize the same part of a target molecule and bind to that specific part [8][9][10]. An antibody is per definition an Y-shaped protein with an important role in the human body's immunity against foreign threats [11]. Antibodies are commonly used by the immune system and have the ability to identify foreign antigens, like viruses, bacteria along with other parasites, but also in neutralizing them.

4.4. Carbohydrates

Carbohydrates are a large group of biomolecules which are in most of the cases sugars and starches. This group of molecules are divided into classes such as mono, di, tri and polysaccharides. Glucose and cellulose are two typical examples of each type [12]. Biomolecules such as carbohydrates are in general molecules with a simple structure and are usually made up by atoms like carbon, hydrogen and oxygen. A characteristics of this biomolecule is the hydrogen – oxygen bond (OH bond). Carbohydrates are essential nutrient used as an energy source in our body.

4.5. Oligonucleotides

Oligonucleotides are a group of biomolecules with a specific general structure. This kind of molecules are known for their short DNA (deoxyribonucleic acid) characteristics [13]. They are simple short single-stranded DNA/RNA molecules (e.g siRNA) which are in most cases built up of approximately 13-25 nucleotides [14]. A nucleotide is an organic molecule composed of the three following components: a nitrogenous base, a phosphate group and a pentose monosaccharide (ribose) [15]. Oligonucleotides are frequently used as probes to detect complementary sequences [14].

4.6. Lipids

Lipids are one of the larger groups of biomolecules which in everyday language are referred to as fats. Lipids are normally divided into a few major subgroups such as fats, oils and waxes. This group of biomolecules have no specific structural characteristics more than the lack of solubility in water due to missing polarity in the structure [16][17]. Lipids can be found in cell membranes as protecting phospholipids, in food as saturated and unsaturated fatty acids, in steroids as hormones, just to mention a few examples.

4.7. Medical Devices

The term medical device covers a great number of products used in medical health care. It ranges from simple items like plasters to more advanced systems such as implants. [18][19]. The products are classified depending on regulations, requirements and three levels of classification. These classes are based on the effectiveness and safety of the device depending on the level of control needed [20]. A combination product is either a drug or biologic that is combined with a medical device. The different combinations are drug-device, device-biologic, biologic-drug and drug-device-biologic [21]. Examples of the different combinations are drug coated implants or delivery of drugs locally [22]. There are requirements for material that are either implanted or injected either in vivo or at contact with the human body – biocompatible, non-toxic, nonallergenic, endure corrosion and should not degrade in vivo. Materials that can be used are metallic compounds, ceramics, polymers and composite materials [23].

4.7.1. Surface Coating, Drug Delivery and Nanotechnology

Surface coatings are used to make implants interact with the body's cells. This interaction is called bio-integration, which essentially prevents harmful effects such as inflammatory response [24]. Drug delivery is a way to achieve therapeutic effect in humans or animal with the help of administering and processing pharmaceutical compounds [25]. Proteins such as collagen, fibroin, silk, keratin, albumin and casein are the leading candidates for surface coatings, tissue engineering and drug delivery. This because of their capacities such as biodegradability, bioresorbability and biocompatibility [26]. Nanotechnology is used in various applications such as biochips, pacemakers, chemotherapy, pumps, and drug delivery systems, it is used to influence the structure and properties at a nanoscale. [27].

5. Results

The results are divided into sections where each class of biologics is presented separately. Each section begins with an explanation of the therapeutical class, including the potential of the class, to then present the market status in the past, current state and how it is expected to change viewed from a future perspective, along with trends within each class.

5.1. Peptide-based Therapeutics

Therapeutic peptides have several advantages compared to other biologics and small organic molecules, e.g. traditional medicines. Due to their smaller size, they have the potential to penetrate further into tissues, they are less immunogenic, and they have a lower manufacturing cost. Peptides, in general, have a shorter half-life which minimizes the risks of systemic toxicity due to a smaller risk of peptide accumulation in tissues. The risk of toxicity is further reduced because the degradation products of peptides are amino acids [28].

5.1.1. Peptide-based Therapeutics: Market and Trends

The decreasing number of approved drugs produced by the pharmaceutical industry has led to increased expenses for the development of novel drugs. This situation has required different approaches to increase pharmaceutical R&D productivity. Due to the many advantages of peptides over other drug candidates, a revival in interest of peptides as novel drug candidates has been seen [28].

There are currently more than 60 FDA approved therapeutic peptides on the market. This number is expected to increase significantly as a result of the approximately 140 peptide therapeutics in clinical trials and over 500 in preclinical development. Due to its intrinsic selectivity and efficacy, peptides are not only playing an important role in human physiology, its properties are also found to represent an exceptional starting point for the design of new commercial therapeutics [29].

Ferring Research Institute is a pharmaceutical company concentrated on R&D of peptide drugs and other biologics. The company is committed to building a portfolio of novel, innovative peptide therapeutics and are therefore investing heavily in the development of creating new therapeutics [30]. At the 11th Annual Peptide Therapeutics Symposium 2016, Ferring Research Institute presented the current status in development trends for peptide therapeutics (in Europe, the U.S. and Japan), see Figure 2 [31].

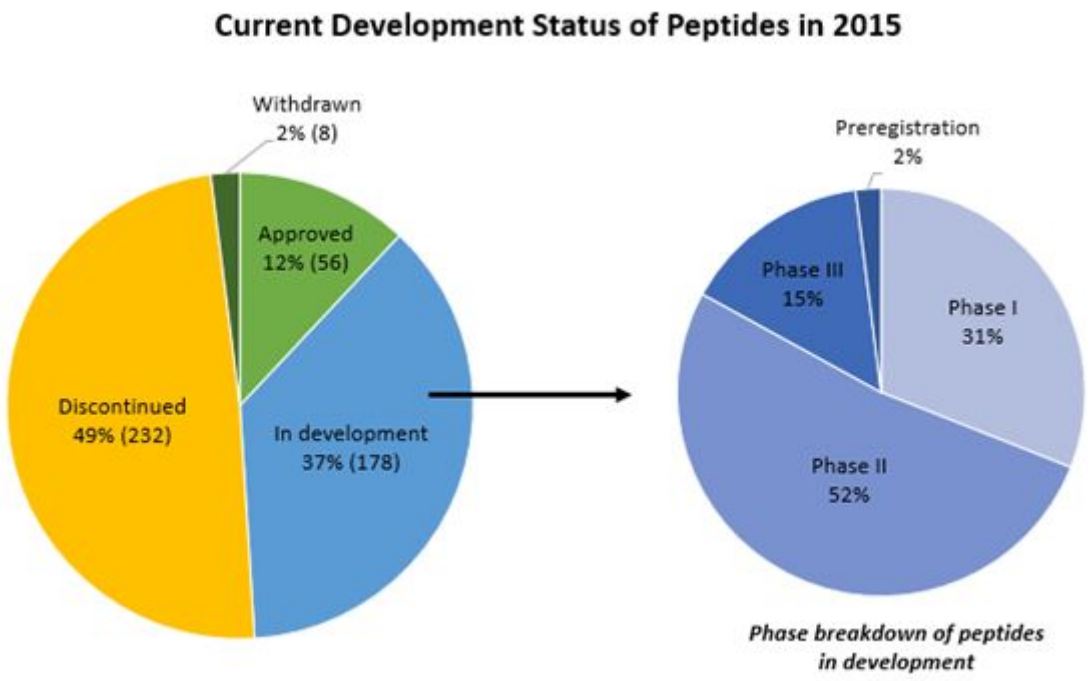

Figure 2. The left diagram shows the status in 2015 of therapeutic peptides regarding the number and share of approved peptides, peptides withdrawn from market, discontinued development and ongoing development. The right diagram shows a phase breakdown of the peptides in development. Insulin products and peptide vaccines are not included.

During the period 2010 to May 2015, over a third (35%) of the peptides that entered clinical trials address metabolic diseases. The second largest treatment area, with 13% of the peptides entering clinical studies during the same period, was oncology [31].

The global peptide therapeutics market is predicted to increase from US$14.1 billion in 2011 to US$25.4 billion in 2018 [32]. Ferring Research Institute have ranked the major key players in the peptide-based therapeutic market based on global sales in 2009 and in 2015 and peptide top sellers in 2015, see Figure 3 [31].

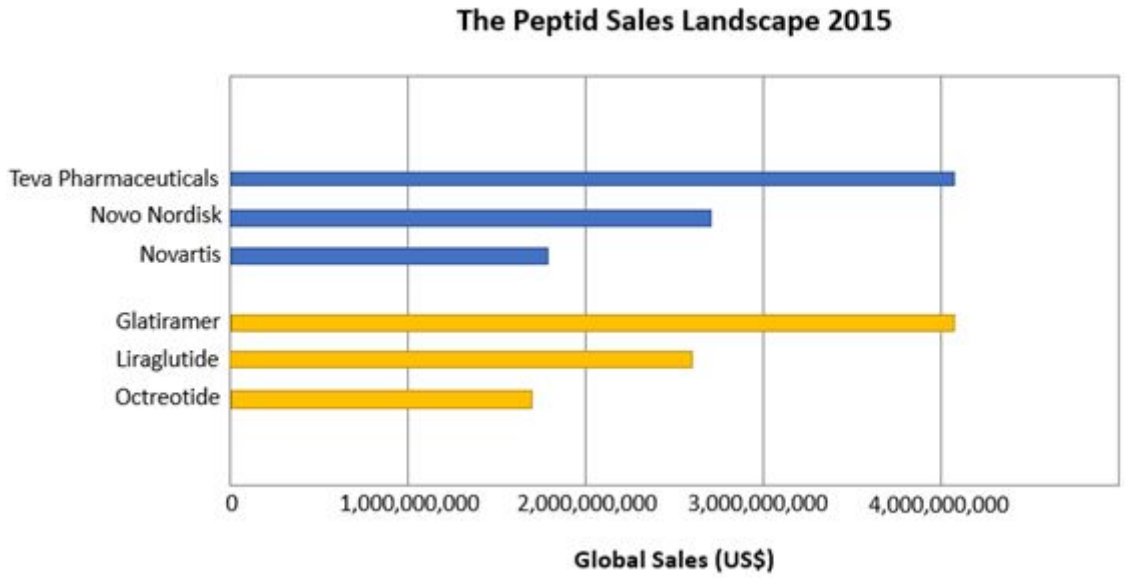

Figure 3. The diagram shows sales for the top three leading companies on the global peptide market 2015 (in blue) and the peptide top sellers 2015 (in yellow). The diagram does not include insulin products and peptide vaccines.

The top three leading companies in the peptide-based therapeutics market in 2015 were Teva Pharmaceuticals, Novo Nordisk and Novartis.

Teva Pharmaceuticals tops the list with global sales over US$4 billion. This correlates with the top selling peptides in 2015 globally; the company's top selling peptide-based therapeutics is Copaxone® (glatiramer acetate), used for the treatment of patients with relapsing forms of multiple sclerosis (MS) [33]. Copaxone® was the top seller in 2015 with global sales of over US$4 billion, see Figure 3. The global sales in 2016 were US$4.223 billion [34]. Analysis predicts decreasing in the global sales of Copaxone®: US$3.64 billion (2017) and $US3.003 billion (2018) due to increased competition [34]. A generic to Copaxone® – Glatopa® – got FDA approval in April 2015 [35]. Glatopa® is provided by Sandoz, a division of the Novartis group [36].

The second leading company on Ferring Research Institute's ranking of the major key players in the peptide-based therapeutics market is Novo Nordisk with global sales over US$2.5 billion in 2015, see Figure 3. This correlates with the top selling peptides in 2015 globally; the company's top selling peptide therapeutics is Victoza® (liraglutide), used for the treatment of patients with diabetes type 2 [37]. Victoza® was the second bestselling peptide-based therapeutics in 2015 with global sales of US$2.524 billion. The global sales in 2016 was US$2.806 [38]. Victoza® got FDA approval in 2010 and EMA approval in the middle of 2009 [39][40].

The third leading company is Novartis with global sales over US$1.5 billion. The company's top selling peptide therapeutics is Sandostatin® (octreotide). Sandostatin® is used to treat different types of disorders that affects the endocrine system, e.g. pituitary tumors [41].

Sandostatin® was the third bestselling peptide therapeutics in 2015 with global sales of US$1.63, see Figure 3. The global sales in 2016 was US$1.646 [42].

Even though peptide-based therapeutics have been extremely successful among other biologics, they cannot be effectively applied to all biological targets and in all diseases. Biologics, in general, are usually not applicable to intracellular targets due to its poor membrane permeability. Peptides are suffering from intrinsic weaknesses, such as poor chemical and physical stability, poor cell permeability and a short plasma half-life. These aspects must be addressed and a promising strategy is to improve the properties of peptides through stabilization and conversion into non-natural structures. This includes the compounds referred to as *peptidomimetics*, see examples in Table 1 below [43].

Table 1. The table shows examples of the new generation peptides.

Peptide class	Example	Target	Therapeutic application	Development phase	Company
Cyclic	Unnamed	Unknown	Immuno-oncology	Phase I	PeptiDream/ Bristol Myers Squibb
	Pasireotide	Somatostatin	Cushing's disease	Approved	Novartis
Stapled	ALRN-6924	HDM2/p53	Oncology	In clinic	Aileron
β-hairpin	POL7080	*Pseudomonas aeruginosa*	Antibiotic	Phase II	Polyphor
Bicyclic	BT1718	Cancer cells (MT1-maytansinoid peptide drug conjugate)	Oncology	Preclinical	Bicycle
Cysteine-rich	Ziconotide	N-type voltage gated calcium channel blocker	Analgesic	Approved	Elan
α/β peptide	LBT 3627	Vasoactive intestinal peptide receptor 2	Neuro-protective	Preclinical	Longevity biotech
Hybrid macrocycle	Unnamed	Inhibitor of apoptosis proteins	Oncology	Preclinical	Ensemble Therapeutics

Signifor® (pasireotide) was approved in 2012 in both the EU and U.S. and is used to treat patients with Cushing's disease [44][45][46]. Pasireotide is a cyclic peptide (Figure 4a) and its cyclic structure is increasing the stability of the peptide due to its reduced exposure to proteases. Some of the novel cyclic peptides in development have demonstrated that oral

bioavailability is possible – naturally occurring peptides are usually not orally available [32][43].

Prialt® (ziconotide) was approved in 2004 and 2005 in U.S. and EU, respectively, and is used to treat severe chronic pain [47][48][49]. Ziconotide is a synthetic version of the cysteine-rich peptide ω-conotoxin MVIIA found in the marine cone snail *Conus magnus*, see Figure 4b [50]. Natural occurring peptides with cysteine-rich structures possesses great thermal and proteolytic stability due to the multiple disulfide bridges. These peptides have, in some cases, also demonstrated significant cellular uptake. A development in this field is the use of cyclotides in which one or several of the loops are replaced with linear, bioactive epitopes, see Figure 5. This offers opportunities to combine an active peptide with the stability, particularly the proteolytic stability, of the cyclotide. There are some successful examples where this grafting technique can increase the ability to address intracellular targets [43].

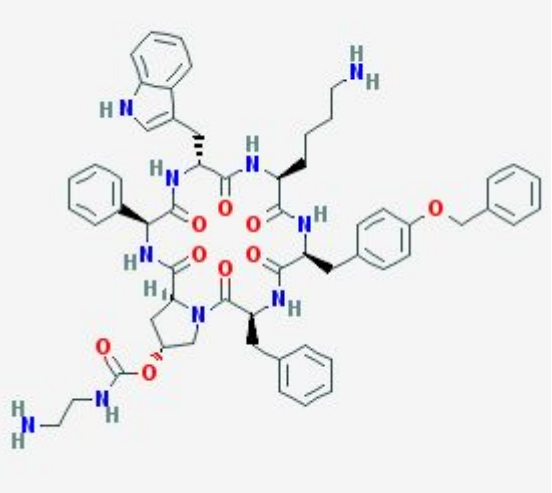

Figure 4a. The figure shows the chemical structure of Signifor® (pasireotide). *Source: https://pubchem.ncbi.nlm.nih.gov/compound/9941444#section=Top*

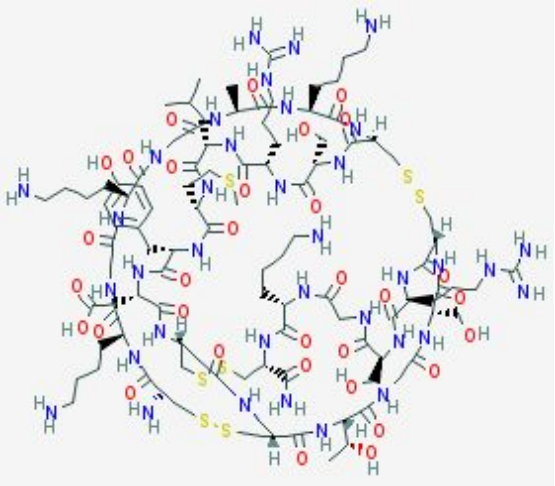

Figure 4b. The figure shows the chemical structure of Prialt® (ziconotide). *Source: https://pubchem.ncbi.nlm.nih.gov/compound/16135415#section=Top*

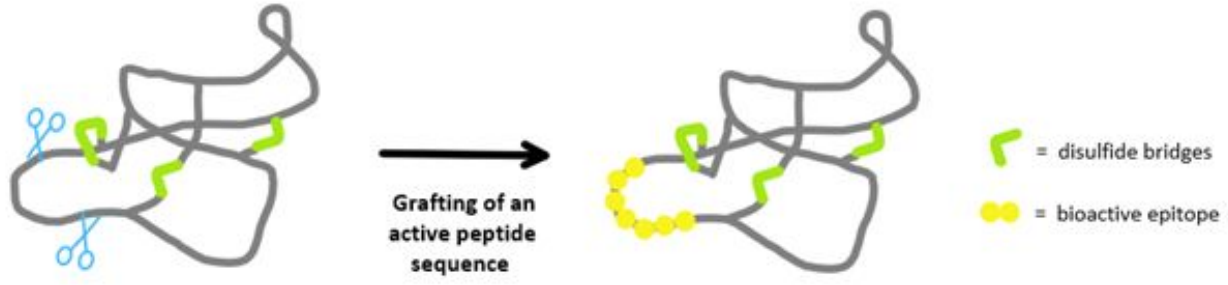

Figure 5. A schematic figure showing how cysteine-rich peptides are grafted with bioactive epitopes.

5.2. Protein-based Therapeutics

This section contains both protein-based therapeutics and its major subgroup monoclonal antibodies.

Proteins

This kind of pharmaceuticals are based on proteins with characteristics that can be used in the medical sector in treatment of various diseases [51]. Proteins are essential for many biological processes in the human body and the lack of proteins will/may disturb the normal cell/tissue function. Drugs based on proteins are in general large, with a peptide-like structure and consists of more than 1000 amino acids linked together by peptide bonds. Structures consisting more than 1000 amino acids gives rise to high molecular weight which can in many cases reach 150,000 g/mol [52].

Monoclonal antibodies

Thanks to the uniqueness of monoclonal antibodies they are widely used in treatment of diseases such as cancer, Rheumatoid arthritis (RA), Crohn's disease and kidney transplant rejection [53][54][55]. Oncology is one of the most successful fields with the conjugated monoclonal antibodies (ADCs), were great efficiency has been observed with the minimized side effects due to the high specificity of the ADCs [56][57]. Monoclonal antibodies are usually divided into evolutionary – and laboratorial designed mAbs. The evolutionary monoclonal antibodies consists of four major antibody types, which then are divided in first, second, third and fourth generation mAbs [58].

First generation:

Murine monoclonal antibodies: Murine antibodies are the most simple antibody type and consists of only one genetic material from a nonhuman source. The used animals as a donor source for this kind of antibody are mice and rats [58]. The biggest consequence of using this type of antibody is that it's foreign to the human body [59]. This will in many cases result in an induced response from our immune system, which in worst case scenario can result in a deadly outcome.

Second generation:

Chimeric monoclonal antibodies: Chimeric monoclonal antibodies are a genetic mixture of materials both from a human but also from a nonhuman species [60]. The most commonly used nonhuman source is a mouse [61]. A chimeric monoclonal antibody does in the most cases contain around two thirds genetic material from a human being (Fc Ig) and one third genetic material from a mouse [58][62]. This specific mixture of two different genetic materials in correct proportions have the properties of reducing the immunogenicity. Immunogenicity is a measurement of the antigens ability to stimulate a development and production of a specific antibody against an antigen of choice. Chimeric monoclonal antibodies have proven to be effective when used in treatment of various autoimmune

diseases but they are also used with coronary artery procedures along with indications for metastatic disease [58].

Third generation:

Humanized monoclonal antibodies: Humanized monoclonal antibodies are also a genetic mixture of two different genetic materials, like the chimeric mAb. The difference between the humanized- and chimeric mAb is the amount of each genetic material [63]. This kind of antibody is produced in a controlled laboratory environment and consists of approximately 90% genetic material from a human being and only a small part of nonhuman material (around 10%) [64]. The source of the nonhuman genetic material is also in this case most commonly a mouse. The specific thing about this kind of mAb is the interaction. The nonhuman part of the antibody binds to the specific antigen while the other part is protected and not prone to interact with the human body's immune system. By avoiding interaction there is less risk that the antibody will be eliminated [65]. Humanized monoclonal antibodies have proven to be successful in treatment of various kinds of diseases. This category of pharmaceuticals have a future potential in treatment and prevention of respiratory syncytial virus (RSV), breast cancer along with treatment of chronic lymphocytic leukemia (CLL) [58].

Fourth generation:

Fully Human monoclonal antibodies: Human monoclonal antibodies are fully synthesized in the laboratory. The name of this specific type of mAbs can in many cases be interpreted incorrectly because these monoclonal antibodies do not need to be isolated from a human. The only human element about this category of mAbs is the fact that they are created from human genes [60]. This means that fully human monoclonal antibodies do not contain any murine part. The lack of murine sequences in the antibody as a result of 100% human genes should result in the majority of cases have a reduced risk of an induced immune response [65]. The first therapeutic under this category was adalimumab also called Humira® provided by AbbVie Inc. Fully human monoclonal antibodies in a future potential in the medical field of oncology. MabVax (company specialized in cancer vaccines) has proven that these specific type of mAbs can be used in cancer vaccines, with currently 8 vaccines on the pharmaceutical market [60].

The laboratorial designed mAbs include two major subgroups. The groups are as follows:

Naked monoclonal antibodies: This kind of monoclonal antibodies are not conjugated with a toxin or a radioactive component/atom [66]. They are "naked" without any compound attached to them [67]. The naked monoclonal antibodies can act as killers, which means that they can kill cells through blocking the antigens on them which results in preventing the specific targeted cells from growing for example [68][69]. The cell killing process can proceed through a induction of apoptosis also called cell death. These antibodies can also act as "markers" [68]. A marker in this case is a antibody with the ability to bind to a cancer cell

and mark it so the human body's immune system can recognize the threat and destroy it [70]. Naked mAbs are widely used in cancer treatments [68].

Conjugated monoclonal antibodies: Conjugated monoclonal antibodies are antibodies that are attached to toxic compounds or radioactive particles [71]. These specific mAbs work as a delivery agent and protector at the same time which decreases the risk of a toxic outcome in the human body [68]. When a conjugated monoclonal antibody is administered into the body, the mAb will search for the specific targeted antigen and deliver the toxic/radioactive substance to the place where the attached compound has the most significant impact [61]. This kind of targeting system lowers the probability for cell damage to normal cells. Conjugated mAbs are also used in cancer treatments [68].

5.2.1. Protein-based Therapeutics: Market and Trends

The most diverse and dynamic role of a macromolecule in the body belongs to proteins. In the beginning of the 1980s a new pharmaceutical class based on proteins appeared. Compared to small molecules they have numerous advantages; impossible to mimic by basic chemical compounds, highly specific action which makes them less probable to interfere with the normal biological process in the body and less likely to induce immune response. Even though protein-based therapeutics are at its infancy they play a significant role in every field of medicine [72]. According to BCC research press release from 2017 for the report, *"Global Market for Bioengineered Protein Drugs Showing Modest Growth"*, the global market for protein therapeutics was estimated to US$172.5 billion in 2016 and is expected to reach US$228.4 billion by 2021. The report includes predictions that the growth of the protein therapeutic market is influenced by a number of components, such as new technologies, patent expiries, growing competition, changing lifestyles and greater investments in development and research [73].

The pharmaceutical company Novo Nordisk is looking into four investigational protein and peptide drugs that are in Phase III clinical trials; an oral semaglutide and a semaglutide for diabetes, Somapacitan for growth disorder and N8-GP for hemophilia. These Phase 3 drugs that are in research pipeline are expected to result in solid growth outlooks for Novo Nordisk [74].

Diabetes is one of the most growing diseases in our society as our lifestyles changes worldwide, an aging population and rises in obesity has increased the demand for insulin therapies [75]. The number of people with diabetes were estimated to be 135 million by 1995 and is predicted to increase to 300 million people by 2025. The increase is expected to be in countries such as U.S., India and China. In industrialized countries the age of the people with diabetes is ≥65 and the age for people with diabetes in rapidly industrializing countries are expected to be 45-65 years old [76].

Monoclonal Antibodies

The monoclonal antibody (mAb) market is the fastest growing market today in biologics, with a market valued to US$85.4 billion in 2015 and which is expected to grow to US$138.6 billion by 2024 [77]. The number of FDA approved therapeutic monoclonal antibodies increases constantly, with three to five new drugs on the market each year. There are currently 52 investigational mAb therapeutics in late-stage clinical studies; 20 of these are for cancer indications, the remaining 32 are for non-cancer indications. If the outcome of these studies is positive, it may enable submission of marketing applications (in 2017 or 2018), or may provide justification for additional studies. This indicates that a large amount of therapeutic mAbs will be approved in the near future, increasing the number of approved drugs to six to nine each year [78].

There are currently over 230 investigational mAb therapeutics in Phase 2 clinical studies. As of December 2016, marketing applications for ten different monoclonal antibody therapeutics are being evaluated by the US Food and Drug Administration (FDA) or European Medicine Agency (EMA) for possible approvals in the US and EU, respectively. Among these ten mAb therapeutics seven are for non-cancer indications and three for cancer indications [78]. According to a study made in 2014, 70 or more monoclonal antibodies will be on the market by 2020 with a market value of nearly US$125 billion [79]. Therefore, the market is predicted to grow with a CAGR of 10%. The best selling therapeutic mAbs on the market today are Humira® (provided by AbbVie), Remicade® (provided by Janssen Biotech) and Enbrel® (provided by Amgen). The annual sales (2011-2016) are presented in Figure 6 below.

A new generation of antibodies, antibody drug conjugates, is predicted to grow at a CAGR of 21.82% from 2017 to 2022 [79]. Antibody drug conjugates (ADC) refer to antibodies with greater properties, such as unique targeting ability from the mAbs and a cancer-killing property from a cytotoxin. The greatest market growth is predicted in North America since a number of drugs are expected to get FDA approval in the next few years [80]. In august 2015 about 50 antibody-drug conjugates were in clinical studies, where half of these were in phase II or phase III development. Oncology and hematology are the most successful fields, where great efficiency has been observed with the minimized side effects due to the high specificity of the ADCs [81].

To this date, three antibody-conjugated have gotten FDA approval — Kadcyla® developed by Genentech, Adcetris® developed by Seattle Genetics along with Millenium Pharmaceuticals and Mylotarg® developed by Celltech Group and Wyeth-Ayerst. Kadcyla is currently dominating the market, but Adcetris is expected to bypass Kadcyla in the future [80][81]. Kadcyla is designed to treat breast cancer and the drug targets the HER2 protein. Adcetris is an antibody conjugated to a chemo drug — MMAE, and developed to treat Hodgkin lymphoma. Mylotarg was withdrawn from the market in 2010, due to a post-approval phase III study that proved no clinical advantages of the drug [82].

ADCs are expected to open doors for new market opportunities as new treatment areas are being evaluated, and the market shares are predicted to grow rapidly. The market is driven by the broad pipeline, the recently approved drugs — Kadcyla and Adcetris, increasing amount of cancer incidents and the novel treatment alternatives the ADCs has to offer, such as a larger therapeutic window [81][82]. An increased amount of antibody drug-conjugates in clinical pipeline was observed in 2016, especially for drugs in Phase II and III development. Through the entire year of 2016, 32 clinical studies were initiated for ADCs. In total, 14 studies entered Phase I, three entered Phase I/II, four advanced to Phase II and two reached Phase III development. Therefore, four ADCs were in Phase III studies in January 2017. In 2017 new market approvals are predicted to become reality — a possible reapproval of Mylotarg with another dosage regimen and the possible approval of inotuzumab ozogamicin for the treatment of acute lymphoblastic leukemia (ALL) [83].

Annual sales between 2011 and 2016 and the estimated annual sale for 2020 for Humira®, Remicade®, Enbrel®, Kadcyla® (ada-trastuzumab emtansine) and Adcetris (brentuximab vedotin) are presented in the diagram in Figure 6 below.

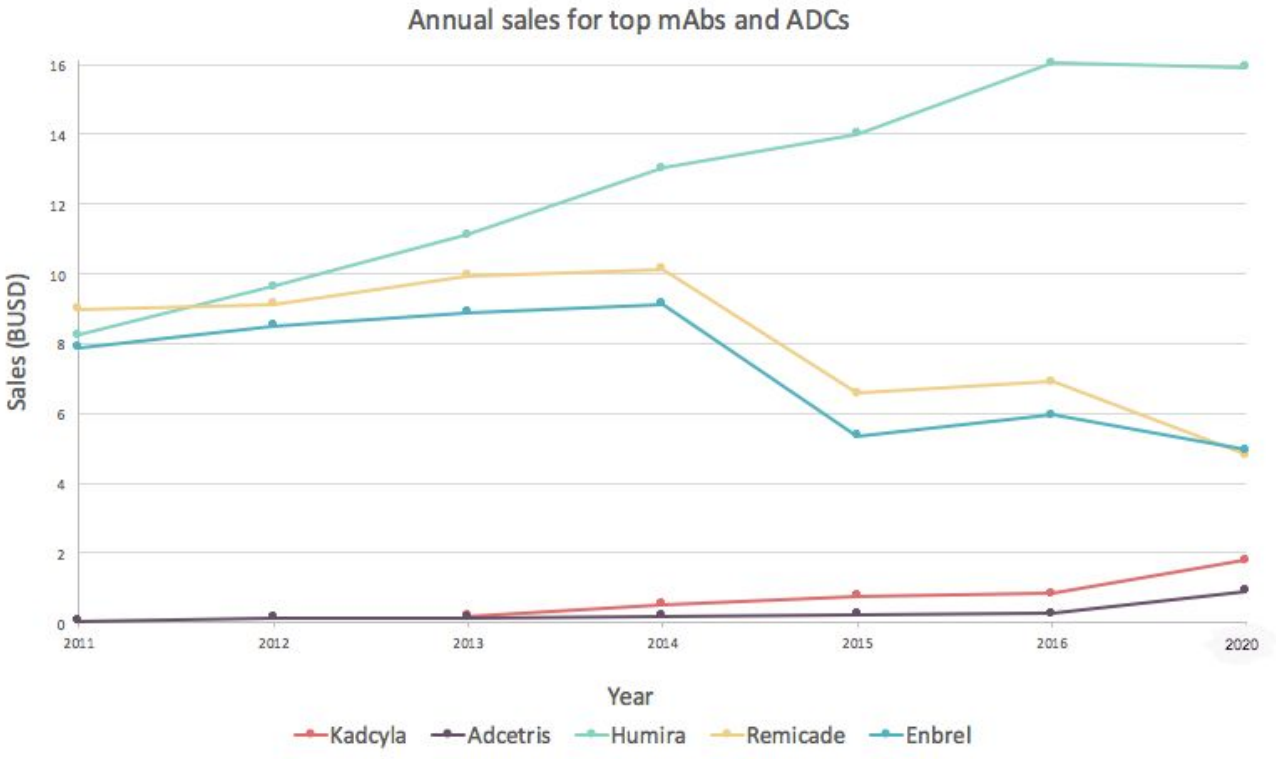

Figure 6. Annual sales (in billion US$, BUSD) for Humira®, Remicade®, Enbrel®, Kadcyla® and Adcetris, from year 2011 to 2016, including the estimated annual sale for 2020. Source: FiercePharma

5.3. Carbohydrate-based Therapeutics

This group of pharmaceuticals is a small group on the drug market but still has a well-known biological drug called Heparin which was already discovered in 1916 [84]. However, it is one

of the few drugs that have been successful within the group. There is still much research going on about carbohydrate-based drugs [85]. This kind of drugs create big problems for pharmacological properties due to the high polarity in the structure and difficulties to manufacture synthetically. Carbohydrate-based biologics have a huge potential and will be a key player in the medical treatment of various diseases in the future.

5.3.1. Heparin

Heparin is a natural pharmaceutical drug with a long medical history, the drug was already in clinical trials during the early 1930s [86]. Heparin has been thereafter widely used in treatment of various thromboembolic disorders as a result of its natural anticoagulant effects/properties. A thromboembolic disorder [87][88], is a condition in which a formation of a blood clot occurs in a blood vessel (for example in any vein or artery) and thereafter breaks loose from the blood vessel's wall. After the clot breaks loose it gets carried by the blood stream until it finds another blood vessel to plug. There are many crucial factors for the development of thromboembolic disorders, the most typical causes are divided into patient-related factors, different kinds of trauma along with surgical factors [89].

Heparin can be found naturally in the human/animal body and is an endogenous mucopolysaccharide which is more often referred to as glycosaminoglycan (GAG(s)). Mucopolysaccharides [90] are defined as long chains of sugar molecules linked together with glycosidic linkages. Heparin usually occurs in the liver, lungs and is released from the mast cells [91] (a specific type of immune cells) when needed.

The pharmaceutical named Heparin is divided into two [91] subgroups which differ in character: unfractionated Heparin (UH) and low molecular weight Heparin (LMWH). The main difference between these drugs is the molecular weight along with the linkages between the sugar molecules. UH has a molecular weight range of 3000 to 30 000 Dalton (Da) and LMWH has in average a molecular weight of 4500 to 5000 Da [92].

Unfractionated Heparin is in general defined as a heterogenous mixture of sulfated [92] polysaccharide chains which results in the large range in molecular weight. The medical anticoagulant properties of Heparin vary with the length of the chains [93], which means that the molecular weight of the molecule has an important role when it comes to the treatment. UH is a very specific kind of pharmaceutical which prevents the blood coagulation process (these drugs are called anticoagulants – blood thinners). A prevented blood clotting results in an unsuccessful coagulation which means that the blood is not able to form fibrous tissue [94] to stop a bleeding for example.

The mechanism of action of unfractionated Heparin is an antithrombin-dependent mechanism [92]. UH impedes the blood coagulation process by primarily binding reversibly (the binding can be terminated and is therefor not permanent) to the active site of antithrombin III and activates it. Antithrombin has the ability to inactivate several enzymes and coagulation

factors. Activation of antithrombin III leads to an inactivation of the enzymatic activity of thrombin (factors IIa, IXa, Xa) [95]. Inhibition of thrombin results in a lack of fibrin peptide release, which impedes the process of fibrin clot aggregation [96]. If the fibrin clot aggregation does not proceed, the blood is not able to coagulate properly.

Low molecular weight Heparin [92] is in general defined as a derivate of heparin [93]. The LMWH is obtained by heparin undergoing either a chemical or enzymatic depolymerization to fragments which in most of the cases are one third the size of the original molecule [92]. The remarkable difference between the UH and LMWH in the medical mechanism is the ability to inactivate thrombin. LMWH pharmaceuticals have lower binding properties which results in a reduced ability to inactivate thrombin [92]. The reduced ability to inactivate thrombin can be explained with the chemical properties of LMWH. The fragments of the molecules are not big enough (<18 monosaccharide units) to stimulate the activation of antithrombin III and inactivation of thrombin. However LMWHs are still capable to inactivate factor Xa and this results in a more gentle prevention of the coagulation.

Low molecular weight Heparin is usually the drug of choice when it comes to the Heparin pharmaceuticals. This is because of the fact that LMWHs have fewer side effect compared to unfractionated Heparin. The fewer side effects is a response to the high bioavailability [97], which means that a high amount of the administered pharmaceutical gets through to the system and can have an impact on it [98]. Higher bioavailability means less daily doses of the medicine compared to the UH. LMWHs also have fewer interactions to plasma proteins due to minimal capacity to bind to Heparin-binding proteins and cells [86]. UH has these interactions and binds to plasma proteins along with a low bioavailability [93]. The result is less bleedings while treated with LMWHs compared to inevitable bleedings when it comes to unfractionated Heparin. However, the most severe side effect of UH is not bleedings but the Heparin-induced thrombocytopenia (HIT) and this is the reason why the LMWHs are preferred even if allergic reactions may occur in rare cases [99].

Data from 38 hospitals in the US has shown that approximately 45% [100] of 3778 patients did receive LMWHs during total hip or knee replacement. This only proves how efficient and important carbohydrate-based LMWHs are in surgical medicine. According to the International Medical Prevention Registry on Venous Thromboembolism, statistics including more than 15,000 patients in 12 countries shows that LMWHs were the most used anticoagulant. This study showed in overall that approximately 34% of the treated patients used LMWHs compared to only 11% who used UH [100].

According to News Medical press release from 2015 for the report, "*Heparin Market – Europe Industry Analysis, Size, Share, Growth, Trends and Forecast, 2014 – 2022 "*, the value of the Heparin market in Europe was estimated to US$2,004.5 million in 2013. The Heparin market in Europe is predicted to grow rapidly in the next few years and reach US$3,148.0 million by 2022 along with a CAGR of 5.2%.

As reported by Job Harenberg MD, professor in Medicine, the global Heparin market was valued to US$ 8.2 billion [101] in 2014 with a high CAGR of 6.3% between the following years 2015 to 2023. The valued market of 2014 is predicted to almost double by 2023 and is estimated to be valued of a total US$14.3 billion [101]. This shows the big potential in this market. Waran® (a Vitamin K-dependent anticoagulant) provided by Takeda Pharma is the the top selling anticoagulant globally and Heparin overall is globally the second bestselling pharmaceutical in this category.

The most used blood thinners worldwide among the LMWHs are Enoxaparin (Lovenox®) along with Dalteparin (Fragmin®). There has been a downfall in annual sales for these pharmaceuticals in the last few years, the downfall can be explained as an outcome of the expiration of all patents of LMWHs in 2008 [101][102]. The expired patents opened the door for development of biosimilars and gave other companies an opportunity to make an impact on the market. After the biosimilars came out in this particular market, they have contributed with many benefits to the health care systems, especially in developing countries [101]. Companies producing biosimilars of bestselling pharmaceuticals as Enoxaparin can offer the same active substance to a lower price which results in a lower treatment price and savings for healthcare. The EMA approved two LMWH biosimilars – Inhixa and Thorinane in 2016 [103][104].

The only controversies of LMWH biosimilars is the approval of the pharmaceuticals. Many continents have a lower standard compared to Europe and North America [101] when it comes to approval of drugs which can in many cases lead to tragic consequences, in worst cases death. The safety and high production standards should always be a priority. Unfortunately, they are not always that.

The price of treatment between UH and LMWH differ depending on which alternative is chosen and which disorder that is treated. When it comes to LMWH-based treatment in one of the most common thromboembolic disorders called VTE (venous thromboembolism). The average cost of LMWH-based treatment with Enoxaparin is US$1,264 per patient [105]. A patient undergoing UH-based treatment of VTE need to be hospitalized under full supervision. The average cost of this treatment is US$1,585 per patient [105]. DVT (deep vein thrombosis) is another common disorder. The average treatment cost of UH-based treatment is US$405,534 compared to US$315,929 with LMWH-based treatment (Enoxaparin), the prices for treatment of DVT are in per 1000 patients [105].

As mentioned before, Heparin-induced thrombocytopenia is a dangerous side effect and it is a 85.2% higher probability to suffer from the side effect when treated with UH compared to LMWH [105]. The treatment of HIT is even more expensive compared to the treatment prices above. The average cost of this treatment is US$3,520 per patient [105]. According to a study

in Germany, the healthcare system saved US$1,687,820 per 1000 patients [106] when patients were treated with LMWH-based treatment compared to UH-based treatment.

Statistics provided by Bayer HealthCare [107] show that the most common cause of death in Europe every year are blood clots. More people die from blood clots than from diseases such as breast cancer and prostate cancer. Trends show that development of thromboembolic disorders among the population in both Europe and North America have increased [101]. According to a recent study, only in France almost 500,000 people develop DVT along with approximately 300,000 deaths each year only in the US and over 500,000 deaths across Europe [108].

5.4. Oligonucleotide-based Therapeutics

The first use of therapeutic oligonucleotides (ONs) started already in 1978, when Zamecnik and Stephenson suggested that oligonucleotides could inhibit the replication of the Rous sarcoma virus. But it was not until 1986, when oligonucleotides were included in studies against HIV, when companies started investing in developing oligonucleotides as drugs [109]. At that time the technique was too challenging and comprehension on a molecular level was missing, which resulted in only a few companies surviving the 1980s and 1990's [110].

It took almost four decades for oligonucleotide-based therapeutics to reach clinical maturity [110]. Today, oligonucleotide-based therapeutics are predicted to show great potential in the treatment of various diseases, especially since more molecular targets are being identified each year. In theory, oligonucleotides can practically target anything through Watson-Crick base-pairing, targets that are otherwise impossible for example monoclonal antibodies [111]. The concept of therapeutical ONs is pretty simple; target RNA with a complementary sequence which modulates gene expression and results in blocking the disease-causing protein. The reality, however, is not that simple. The delivery of the drug to the right organs and cells in the human body have been a major obstacle in the development of therapeutic ONs. Accordingly, targeted delivery is of great importance and methods including different types of drug conjugates are currently being evaluated [110][111][43].

There are a number of different oligonucleotide class of drugs – antisense oligonucleotides (ASOs), small interfering RNA (siRNA), aptamers among others [111]. Of today's five FDA approved therapeutic oligonucleotides, four are ASOs and the last one is a aptamer. There are however several ongoing studies for siRNA based therapeutics, where great success has been observed with targeting the liver [110].

Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) are synthetic strings of DNA/RNA monomers that bind to the RNA-strain and suppress its function. ASOs target RNA with the use of Watson-Crick base-pairing and can target either microRNA (miRNA) or messengerRNA (mRNA), affecting the RNA splicing or the degradation of mRNA, respectively [43]. Unlike conventional drugs,

which bind to proteins, ASOs alter the gene expression (mRNA translation) which results in blocking the action of a specific protein. This gives huge potential in the treatment of chronic and genetical diseases, since they slow or halt the disease progression [109]. The first antisense oligonucleotide, fomivirsen, got its FDA approval in 1998, but was withdrawn from the market a few years later [112]. Today, in total four antisense oligonucleotides (including fomivirsen) have gotten FDA-approval and there are multiple drugs in ongoing clinical trials.

Small Interfering RNA

Small interfering RNA (siRNA) is a double stranded RNA sequence that binds to the RNA-induced silencing complex (RISC). The RISC complex is formed during the transcription process when microRNA binds to argonaute protein and the complex is responsible for the gene silencing phenomenon, also called RNA interference (RNAi). The ability to affect gene silencing has resulted in huge investment in this pharmaceutical field [43]. Today, there are not any FDA approved siRNA-based drugs, but there are potential drugs in the pipeline, for example for hepatitis B [110]. Targeted delivery has been a huge obstacle in the development of siRNA-based therapeutics, but conjugation to lipids or carbohydrates could solve the issue. Lipid nanoparticles have shown to accomplish efficient delivery to different tissues in the body and conjugation of cholesterol or other lipophilic agents to siRNA have proved to improve gene silencing in the tissues [110][43].

Conjugation of siRNA to N-acetylgalactosamine (GalNAc) has shown great results in suppression of gene expression when targeting the mRNA in the liver. GalNAc is a high affinity and highly effective ligand for the asialoglycoprotein receptor, which is present in the hepatocytes. Conjugated siRNAs offer more stability towards nucleases and more advanced pharmacokinetics than the unconjugated [110][113]. The majority of the listed clinical trials for siRNAs are for cancer-indications, others target mainly the liver and the eye [114].

Aptamer

Aptamers bind to small and large molecules — mainly to proteins, and are unlike other ON-based drugs that bind directly to the RNA-strain [43]. They have a really high specificity and affinity, which depends on their ability to form three-dimensional structures [114]. Their main function is to modulate a certain protein function. The first and only FDA approved therapeutic aptamer is pegaptanib, which was approved in 2004, but a number of potential drugs are in ongoing clinical studies. Aptamers have also been used as drug delivery systems for oligonucleotides, with either conjugation/hybridisation directly on the therapeutic ON or with other techniques such as nanoparticles with the aptamer on the surface [43][114].

The length in nucleotides, if the strain is single or double, target, function and FDA approved active substances of antisense oligonucleotides, small interfering RNAs and aptamers are summoned in Table 2.

Table 2. Summary of three different oligonucleotide types [43].

ON Type	Length (nucleotides)	Single/ double	Target	Function	FDA approved active substances
Antisense ON	16-20	Single	-mRNA sequence -RNA-induced silencing complex	Inhibits gene expression (mRNA translation) by Watson-Crick base-pairing	Fomivirsen Mipomersen Nusinersen Eteplirsen
siRNA	20-25	Double	RNA-induced silencing complex	Halts translation by mRNA degradation	None
Aptamer	15-60	Single	Proteins	Modulates protein function	Pegaptanib

Modifications of Therapeutic Oligonucleotides

Therapeutic oligonucleotides pharmacokinetic properties, meaning the drug delivery, can be regulated with the chemical structure. Chemical modifications with sugars, backbone phosphate linkages and other non-ribose modifications affect the binding affinity, nucleic resistance, cellular uptake among others properties [43][115]. These modifications are the key to successive drug delivery. In the early stage of the therapeutic ONs, developers and scientists did not take this into consideration and unmodified compounds were rushed into clinical studies. This is one of the contributing factors that led to the downfall of therapeutic ONs in the early 2000s. Today, the further understanding at a cellular level and achievements *in vivo* behaviour have led to clinical efficacy and a broad pipeline [110].

There are a number of different types of modifications; phosphoramidate- and phosphorothioate-linkages, 2'-OMe sugar- and 2'-MOE-sugar modifications, PMO modifications among several others. The phosphorothioate (PS) backbone modification is one of the most successful modifications, which led to the first generation of antisense ONs. Most importantly, this modification supports the RNase H cleavage process and provides both protection to the nucleases and good cellular uptake. The sugar modifications are also frequently used when designing therapeutic ONs and are called the second generation of oligonucleotide modifications. Unlike the PS backbone, the sugar modifications improve both the binding affinity to target and the resistance to nucleic degradation. However, they do not support RNase H cleavage [43][115]. Several ongoing clinical trials carry the 2'-MOE modification, along with the FDA approved drug Kynamro (mipomersen) [110].

5.4.1. Oligonucleotide-based Therapeutics: Market and Trends

The global oligonucleotide (ON) market is one of the fastest growing biological markets today – together with peptides and monoclonal antibodies. The synthesis market is expected to reach US$2.2 billion by 2021, an increase of US$900 million from 2016 [116]. This is mainly caused by the major growth in the life science field and increasing investments from the government. The oligonucleotide market is very hard to estimate, even though everything points to a promising future. The synthesis market is expected to grow with a CAGR of 10.1 percent to year 2020 [117]. Therapeutic oligonucleotides have also shown promising results in treatment for several diseases, such as Duchenne muscular dystrophy (DMD) and autoimmune disorders which are in other cases very troublesome to treat [114][117]. Seven out of ten deaths in the United States are caused by a chronic disease and 86% of the health care costs were accounted by chronic diseases in 2016. In addition, about half of the American population is expected to suffer from a chronic disease [118]. The applications for oligonucleotides expand within time and the most vital fields are: diagnostics, therapeutics, human identity testing, genomics, cloning, genetic engineering, synthetic biology etc [116].

Therapeutic oligonucleotides have a huge future potential because of the advanced technology and further understanding of diseases on a molecular and cellular level. ONs are, as mentioned, short chemically modified strands of DNA and RNA which makes them easy to synthesize on a commercial level. Since therapeutic oligonucleotides interfere with RNA on a cellular basis specific genes can be targeted and therefore regulated, manipulated and even suppressed. This gives opportunities to target the human immune system and modify it, which offers great possibilities to treat autoimmune diseases [117]. Short interfering RNA (siRNA), 20-25 base-pair long double stranded RNA, can also target and suppress gene expression by interfering with the endogenous microRNA (miRNA) system. Even though siRNA is very potent the delivery of double-stranded RNA is much more demanding than with single-stranded. This technique was discovered in 2006 and there are numerous ongoing clinical studies with siRNA targeting therapeutics [119].

Currently there are only four FDA approved therapeutic ONs on the market; Kynamro (mipomersen), Spinraza (nusinersen), Exondys 51 (eteplirsen) and Macugen (pegaptanib), and 142 are in ongoing clinical trials listed on ClinicalTrials.gov. Three of the FDA approved drugs on the market are antisense therapeutic oligonucleotides (ASOs) – Kynamro, Spinraza and Exondys 51, and Macugen is an ON aptamer. In total, antisense oligonucleotides account for 83 of the ongoing clinical studies, where the main indication is cancer with 70 percent of the ongoing studies. Of these 83, ten are in late-stage clinical studies, where six are for cancer indication [120]. Other indications are HIV, Rheumatoid Arthritis, Mesothelioma and conditions that accumulates in the eyes and the liver [117]. In comparison to today's 83 antisense oligonucleotides in clinical development, only 45 were in clinical studies in May 2016 [112]. This is nearly a duplication, indicating a high growth rate of the antisense oligonucleotide therapeutics.

A historically interesting antisense oligonucleotide is Genasense (oblimersen) developed by Genta Incorporated. The drug was designed to treat several types of cancer, such as bladder cancer, breast cancer and lymphoma, by making the cancer cells more sensitive to chemotherapy. The company also suggested that the drug blocks a certain type of protein that makes cancer cells long-lived, but this has not been confirmed in the clinical studies [121]. The drug granted great hope for oligonucleotide-based therapeutics market in the mid 2000s and its downfall resulted in a dip on this medical field [110]. Genta Incorporated went out of business in January 2016 and oblimersen still accounts for 19 of the 58 ongoing clinical studies for cancer indications [120][122].

The leading company in the development of therapeutic oligonucleotides is Ionis Pharmaceutical. The company has dedicated their entire existence to the development of therapeutic antisense oligonucleotides (ASOs) [117]. In 1998 FDA approved their first therapeutic antisense oligonucleotide Vitravene (fomivirsen) against Cytomegalovirus retinitis (CMV) in immunocompromised patients, but the drug was withdrawn due to commercial reasons from the US and EU market in 2006 and 2002, respectively [112]. With Ionis currently two FDA approved drugs – Kynamro® and Spinraza®, their future looks promising. Kynamro®, that got FDA approval in January 2013, is designed to treat patient with homozygous familial hypercholesterolemia (HoFH), an inherited type of high cholesterol. The drug interferes with a mRNA sequence and suppresses the synthesis of apolipoprotein B-100 in the hepatocyte. Kastle Therapeutics acquired recently the full rights to develop and commercialize Kynamro in the future [123]. Kynamro was expected to be the comeback of oligonucleotide-based therapeutics, but the poor marketing and the fact that mipomersen failed to get regulatory approval in Europe, has led to a low market sales. The global sales of mipomersen sodium are US$2.56 million and in total 125 prescriptions have been reported in the US [124].

Ionis Pharmaceuticals announced their fourth collaboration with Biogen in 2013, combining Ionis' leading expertise in antisense technology and Biogens' competence in neurology. The collaboration have resulted in the first therapeutical drug, Spinraza® (nusinersen), towards Spinal Muscular Atrophy (SMA) for pediatric and adult patients, which got FDA approval on December 23, 2016. Spinraza is an antisense oligonucleotide developed to target a specific intron sequence which interferes with the SMN2 exon 7 splicing that leads to SMN protein deficiency [123][125]. The companies present promising data from the interim analysis of the late-stage Phase III studies CHERISH and ENDEAR. The clinical studies grant great hope for the SMA community, showing improvements on the motor function in the patients where some have achieved breakthroughs such as the ability to sit without assistance [126]. Today, Biogen holds the licence of Spinraza and is responsible for future commercialization and manufacturing of the drug. The company has recently filed for authorization on the European, Canadian, Australian and Japanese markets. In addition, the EMA's Committee for Medical

Products for Human Use (CHMP) has granted an Accelerated Assessment status for the drug [126].

Ionis Pharmaceuticals have focused on producing drugs for orphan diseases – diseases with few or no therapeutical options, and they have two potential drugs in the development, IONIS-TTR_{Rx} and volanesorsen, which they believe are close to commercialization [117][127]. IONIS-TTR_{Rx} is developed to treat patients with TTR amyloidosis, a fatal disease with a progressive buildup of an abnormal deposit, amyloid – a plaque that accumulates in organs and tissues around the body. The drug is currently in Phase III studies for patients with confirmed Familial amyloid polyneuropathy (FAP). Both US and EU regulatory agencies have granted Orphan Drug Designation for IONIS-TTR_{Rx}. The company hopes to initiate studies for Familial amyloid cardiomyopathy (FAC) and for senile systemic amyloidosis (SSA), types of amyloidosis that accumulates in the heart [127][128].

Volanesorsen is a antisense drug currently in Phase III studies for the treatment of familial chylomicronemia syndrome (FCS) and familial partial lipodystrophy (LPL). The drug is developed to reduce the amount of apolipoprotein C-III in the bloodstream, which in turn lowers the amount of triglycerides and therefore reduces the risk factor for pancreatitis. Apolipoprotein C-II is a protein produced in the liver that controls the level of triglyceride in the blood. High levels of triglyceride can result in diabetes 2, cardiovascular diseases and even heightened amount may result in acute pancreatitis. Both FDA and EMA have granted Orphan Drug Designation for volanesorsen, which is currently in the hands of Akcsea Therapeutics, a company owned by Ionis. In march 2017 their Phase III study APPROACH was completed, with promising results, and the company is preparing to file regulatory affair submission in the U.S, EU and Canada this year [123][129].

Ionis Pharmaceuticals, together with other companies — including Roche, Bayer, Novartis, AstraZeneca etc. — have several antisense drugs in the development, mainly for rare and severe diseases. Such as Alicaforsen for Pouchitis, which is very close to FDA approval and commercialisation. Other indications for the antisense drugs currently in their pipeline are Huntington's disease, Acromegaly, Amyotrophic lateral sclerosis, each drug in Phase II studies, and Hereditary Angioedema and Alport syndrome in phase I studies. Ionis have also ongoing studies for antisense drugs for cardiovascular diseases, cancer and prostate cancer, different types of hepatitises and metabolic diseases, such as diabetes [123].

GalNac conjugates to siRNA can practically be applied to any disease that accumulates in the liver. They are predicted to be a potential treatment option and cure for chronic hepatitis B virus. There are currently four drugs in human clinical testings, where two of them are siRNA conjugates. Ionis is one company developing GalNAc conjugates for the treatment of hepatitis B virus, where IONIS-HBV-L_{Rx} is currently in phase II studies [110]. Alnylam Pharmaceuticals presented in March 2017 promising pre-clinical data from a mouse-study for a combinational RNAi/vaccination for the virus, and the company believes this approach has

a great future potential [130]. The company does not only have several ongoing studies for GalNac conjugates, but also ongoing studies for lipid conjugated siRNAs, for example a phase III study for the treatment of TTR amyloidosis [110].

The FDA approved Exondys 51 (eteplirsen), produced by Sarepta Therapeutics, in september 2016 for Duchenne muscular dystrophy (DMD). Exondys 51 is the first therapeutical drug towards DMD and is designed for patients with confirmed mutation in the DMD gene that is amenable to exon 51 skipping, affecting 13 percent of the DMD population. The drug is a 30-mer phosphorodiamidate morpholino antisense oligomer (PMO), a synthetic DNA/RNA sequence where the naturally occurring ribofuranosyl rings are replaced with morpholino rings, and the drug binds to exon 51 in dystrophin pre-mRNA [131]. There were contradictions about the approval since eteplirsen had not yet proven to improve the motor function in patients, but the FDA took the fatal disease and the lack of therapeutical options into consideration and granted accelerated approval for the drug [132]. Joseph Schwartz, a leerink analyst, states that the pricing of Exondys 51 might be a concern, since the average cost will lie in the $300,000 class and government programs will not be able to provide a reasonable discount of the price [133].

The first therapeutic aptamer, Macugen (pegaptanib) – developed by OSI Pharmaceuticals and Pfizer, was FDA approved in 2004. The drug is designed to treat neovascular (wet) age-related macular degeneration. Pegaptanib bind to the VEGF isoform and inhibits VEGF165 – a protein – binding to its VEGF receptors [134]. The market sales of the drug increased successfully until 2010. After 2011 sales began to decrease due to the recently approved drug, ranibizumab (mAb), which was a much more effective treatment alternative [135]. A summary of the FDA approved therapeutical ONs is listed in Table 3 below.

Table 3. Approved oligonucleotide therapeutics, indication, target, function and price.

Drug Generic name ON type	Status Year of approval by FDA / EMA	Indication	Target	Function	Price
Vitravene Fomivirsen Antisense ON	Withdrawn 2006 / 2002	Cytomegalovirus retinitis	CMV gene UL123, mRNA	Blocks translation of mRNA, which codes to CMV protein IE2	Withdrawn
Kynamro® Mipomersen Antisense ON	Yes / No 2013 / -	Homozygous familial atrophy	ApoB-100 mRNA	Cholesterol-lowering medication, reduces low density lipoprotein and LDL	20,440 US$ per prescription [122]
Spinraza™ Nusinersen Antisense ON	Yes / Under validation 2016/ -	Spinal muscular atrophy	Exon 7 of SMN2 transcript	Treats SMA caused mutations that leads to SMN protein deficiency	US$125,000 per injection US$750,000 first year of use Then, US$375,000 each year[136]
Exondys 51 Eteplirsen Morfolino ASO	Yes / No 2016 / -	Duchenne Muscular Dystrophy	Exon 51, pre-mRNA	Exclusion of exon 51 skipping during mRNA process, prevents production of dystrophin protein	US$300,000
Macugen Pegaptanib Aptamer ON	Yes / Yes 2004 / 2005	Neovascular (wet) age-related macular degeneration	VEGF isoform	Inhibits VEGF165 binding to its VEGF receptors	5,300 US$ for 5 vials [135]

A summary of the development and market value of therapeutic ONs through the years is presented in Figure 8.

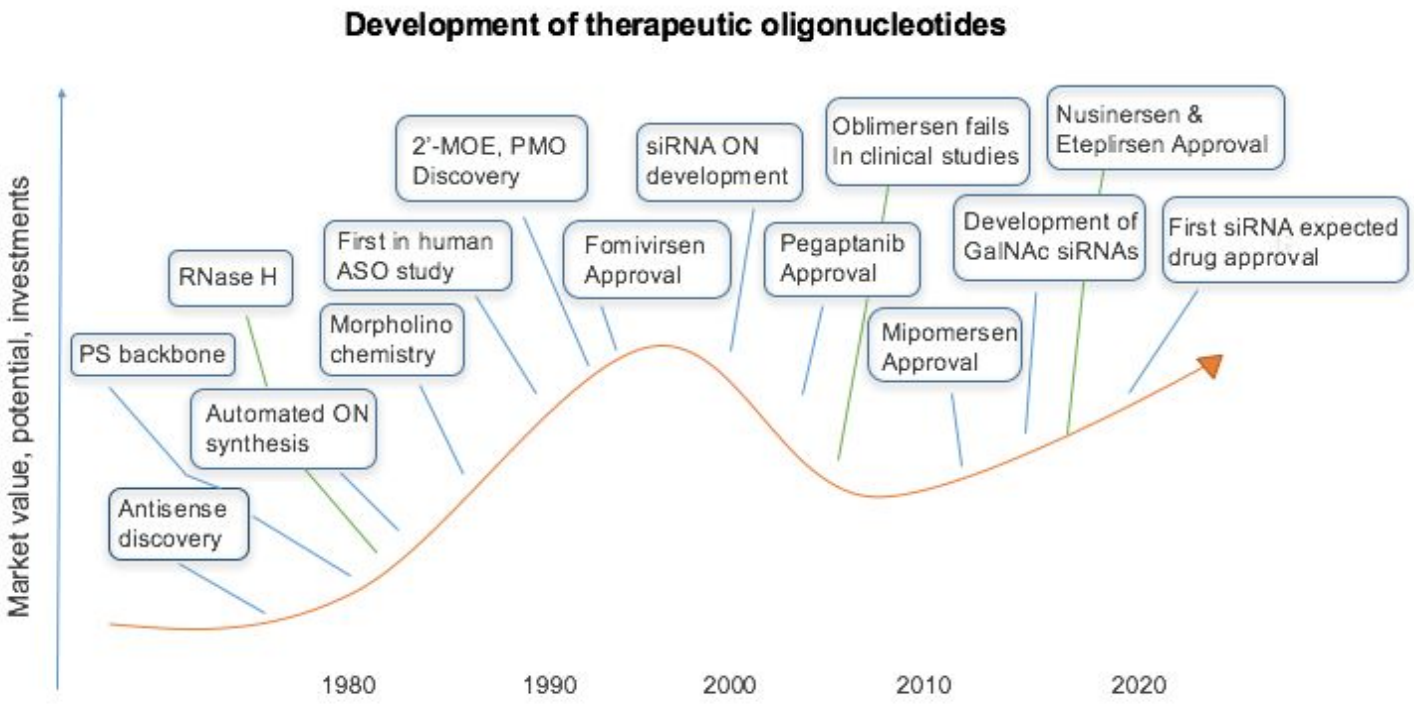

Figure 8. The development of therapeutic oligonucleotides from ~1976 – 2020 [110][115].

5.5. Lipid-based Drug Delivery

Lipid based drug delivery systems have received huge interest because of the enhanced properties of a drug when lipids incorporate a therapeutic. Lipids possess numerous advantages as drug delivery systems in many ways — enhanced bioavailability of poorly water-soluble drugs, toxicity levels reduced, drug release potential increased, better controlled targeting and other qualities [137]. The enhanced specificity of a drug when configured with lipids have created novel platforms in cancer treatment — the low specificity of traditional antidrugs gives serious side effects hence affects the patient's life quality negatively. There is a specific categorization of lipid nanoparticles that are becoming the promising concept in the oncology field, the nanostructure lipid carrier. [138].

There are many ways and investigations in how to incorporate lipids to an active substance. Liposomes are spherical vesicles and coats the active substance usually with a bilayer of phospholipids. They were introduced in the 60s as an idea and later developed, in the mid 90s the first lipid-based drug delivery reached the market under the trade name Doxil(R). The lipid nanoparticles are an alternatively colloidal drug delivery and are divided in three categories: Solid lipid nanoparticle (SLN) are composed by a solid lipid matrix with the drug interposed. Nanostructure lipid carrier (NLC) are based on a core matrix composed of solid and liquid lipids, the drug is introduced in the matrix. Lipid drug conjugates (LDCs) are commonly coupled to oligonucleotides as mentioned in the "Journal of the American chemical society: Multivalent N-Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing". LDCs makes great

difference when targeting. A study concluded that cholesterol-siRNA exhibited a reduction of 50 % mRNA of apoB compared to no effect at all with the unconjugated siRNA [139]. The NLCs are the next generation of SLN mainly because of the better improvement of solving hydrophobic therapeutics [140].

The first application of lipids as drug delivery in pharmaceutical therapy was in cancer treatment and some pharmaceuticals are presented in the text. The lipid carriers gives promising improvement and sometimes complete existing novel drugs being in the pipeline that still don't fulfill the criteria for commercial use.

5.5.1. Lipid-based Drug Delivery: Market and Trends

FDA approved the first lipid carrier therapeutic Doxil® in 1995 to treat ovarian cancer. It is distributed and marketed by Janssen Product. Injected intravenously, the active agent is doxorubicin with a coated lipid bilayer. The liposome avoids detection from the body's immune system and thus increases the circulation time of the drug in the body [141].

The sale of Liposomal doxorubicin based drugs had a value of US$814.6 million in 2015 and the forecast to year 2024 are expected to grow with a CAGR of 6.2 % and reach US$1.38 billion. Doxil® is one of various liposomal based doxorubicin pharmaceuticals accounted in the estimated forecast, but is the largest contributing group. The treatment of breast cancer held a revenue share at about 21.1 % in 2015 and is the main application. The CAGR with highest value is liver cancer treatment and arise from the demand of the drug over other currently existing, to use in chemotherapies [142].

Ambisome® is used for treating fungal medication. It is injected intravenously and the active agent is amphotericin B, coated with single bilayer liposomal [143].

Abelcet® Treating fungal infection. The active agent is also amphotericin B but has got a lipid complex structure, thus not the same as liposome. It is injected intravenously.

Remarks: Ambisome vs. Abelcet in clinics, restricted to the US.
To cut down hospital costs for treatment of invasive antifungal infection by replacing liposomal amphotericin B (ambisome) with amphotericin B lipid complex (ABLC, Abelcet). The study conclude that this replacement would cut down the costs comparing the numbers $US16,748 to $US14,563 with use of ABLC [144].

Pipeline
Lipid Therapeutics Corporation are about to launch a new lipid based drug for Ulcerative Colitis treatment, LT-02, with active substance being Phosphatidylcholine. The drug was in phase III clinical study 2015 according to a report [145]. Worth to mention about Ulcerative Colitis therapy is that a market growth from US$1.7 billion in 2010 is estimated to reach US$3 billion the next decade according to a study from 2012 [146]. It also stated that sale of

LT-02 can reach a value of US$400 million a year. LT-02 will together with other pharmaceutical such as Xeljanz, ozanimod hydrochloride, anti-interleukin antibody Stelara, that are concentrated in treatment of ulcerative colitis, reach a sale of US$6.58 billion by 2025 compared to $5.64 billion in 2015. Meaning a CAGR of 1.6% according to data from GlobalData and analysis [147]. This disease is expected to prevail by time as new drugs arrives in the market. The market of this specific therapy can be found in countries such as the US, Japan, Spain, Germany, France, Italy and the UK.

5.6. Medical Devices

5.6.1. Medical Devices: Market and Trends

Drug delivery systems, biological-device combinations along with personalized medicine drug-devices are included in the combination product market. This also includes nanotechnology, therapeutic/diagnostic treatment products for various kinds of disorders. The market is growing rapidly with focus on niche products which are appealing to a lot of startup capitals for development companies and R&D. The market of combinational products and its development goes hand in hand with the sector of drug delivery system. The combinational market was valued to be US$66 billion in 2012 and is expected to grow to an astonishing value of US$115 billion to year 2019, the growth is expected to be at a rate of CAGR of 7.9 % between years 2013-2019. Biologics and drugs are a complement to the medical device and is a smaller segment of market. Due to combinational products contribution in advance medical health care they are over the years expected to have a large-scale impact. The advantages of these products are several, from improving the patient's compliance, shortening hospitalization, control drug release and provide target delivery to reduce unfavorable side effects. Some of the leading products on the market are infusion pumps, drug eluting stents, wound combination products, photosensitizer, orthopedic combination products, inhalers, and implants. For example there are drug covered implants that relieves pain and heal faster. The mortality is decreasing, which in terms of that is driving a growth in the combinational product market. The combinational products will eventually enable more effective and safer technologies [22].

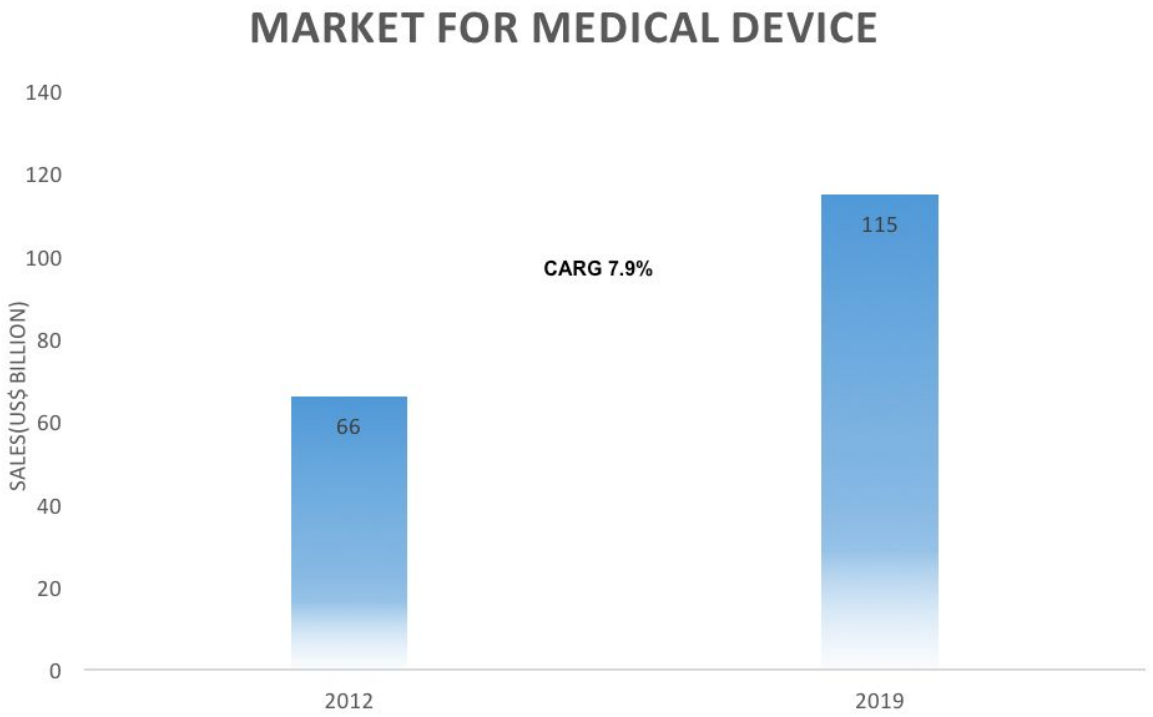

Figure 10. The market sales for medical devices year 2012 and anticipated year 2019.

Drug delivery - Nanomedicine

The market for nanomedicine by itself and as combination based products are predicted to reach at least US$95 billion by 2019, and with an annual growth rate of 12-15%. More than a third of biotechnology companies are starting projects with monoclonal antibodies. This trend implies that a large segment of the nanomedicine market is expected to include therapeutic monoclonal antibodies. At year 2012 this sector was calculated to produce US$31 billion. Crystalline nanomedicine and polymer-based drugs are also major segments in the nanomedicine market. In 2016 the anticancer product market and central nervous system nanomedicine global market was anticipated to reach US$12.7 and US$29.5 billion, respectively. Research in this field is large, with 1,500 applications for patents and 22,000 scientific publications [22].

During 2016, the nanotechnology drug delivery market was growing at an annual rate of 84.79% in US and the global market at a rate of 73.97%. This because the demand on personalised medicine is increasing, models of drugs based on the individual's unique immune response and genome are more frequently used. Nanoparticles used to deliver drugs to specific cells are one of the most significant applications used in nanotechnology medicine. Studies have been made on nanomaterials which have revealed the toxic effects that such materials can cause and the lack of FDA directions are two major causes that could lead to hinders for the nanotechnology market growth [148].

3D-printing

The major trends in the medical device market as the technologies advance are many, 3D-printing is one of the leading trends. For a surgeon to prepare and create anatomical models of a patient's anatomy and even to create new tools, additive manufacturing is playing an significant role. This opens new doors to a market for individualised medical healthcare. Biopharmaceutical companies like Strykes and Johnson & Johnson are investing in 3D-printing [149].

According to *IndustryARC* market research report, which was reviewed by *3DPRINT.com*, the healthcare market for 3D-printing earnings was in 2014 recorded to be US$487 million dollars and is predicted to annually grow at a rate of 18.3% until year 2020. For medical 3D-printing materials alone the earnings was recorded to be US$284.7 million dollars and is calculated to grow at a quicker annual rate than for the rest of the industry. Until 2020 the market for medical and dental 3D- printing is predicted to grow at a rate of 19.1%. On top of this ongoing development of 3D-bioprinting is advancing tissue engineering. Bioprinting will open the doors for tissue and transplantable organs, this reality is not so far away. The leading user of healthcare 3D-printing technology 2014 was North America followed by Europe and last Asia-Pacific [150].

Surface coating

According to the news website WPSD LOCAL6 that made a coverage of the report published by Grand View Research – by year 2025 the market for cell culture protein surface coating is anticipated to reach a value of US$1.3 billion dollar. The CAGR of the period 2017-2021 is at 13.20% [151]. Some of the reasons for this prediction are that focus on stem cell research is increasing and the up and coming demand for products like vaccines, proteins and antibodies [152].

Antimicrobial coating

Infection are a great risk when having implants: therefore, the demand for antimicrobial coatings are increasing [153]. Every year in the US, the number of patients that got infected by hospital acquired infections (Hai) are around 2,000,000 patients where 100,000 infected patients results in death, this according to Center of Disease Control and Prevention [154]. An example biologics used for antimicrobial coating is peptides such as Cateslytin which are used combined with hydrogels such as alginate (anionic polysaccharide) that are designed as matrices, to prevent infections that often emerges in moist environments. The matrices are coated with the combination of hydrogels which has good adhesive properties and catestylin that has antimicrobial properties [153]. The market for antimicrobial coatings for medical devices are anticipated to reach US$1.17 billion dollar by 2020 and during the period 2015-2020 to grow with a CAGR of 14.2% [155].

5.7. Biological vaccines

This section of the report is an extension from the original version and should be interpreted as a general overview. Biological vaccines are starting to become more important with the increasing mutation trends among animal-transmitted viruses. Vaccines of this type usually consist of antigens isolated from bacteria that have been conjugated with biomolecules such as proteins. The market for biological vaccines is very wide and can increase by 1000% from day to day. This growth is driven by the demand, if an outbreak occurs, the market will increase substantially. There are no current global value for this market due to few vaccines available on the market.

The following viruses — Zika and Dengue — were selected because of their uniqueness and to give an insight in how the background and spread of the viruses affects today's society. Another reason behind the choice was to gain more detailed knowledge about how Zika and Dengue managed to survive for decades without being wiped out.

Zika virus

Many animals carry highly dangerous viruses that are incurable still and in many cases lethal to mankind. Viruses such as the Zika virus and dengue fever have taken the world by storm with their rapidly spread across the earth. These animal-transmitted viruses mentioned above are mosquito-transmitted viruses by a specific species called Aedes [156].

The Zika virus has a long history which is dated back to 1947 in Uganda where the first cases were reported [157]. The virus is transmitted through a bite of an infected mosquito, it can also be transmitted through blood transfusion, pregnancy from mother to child (the mother is infected and passes the virus on to the child) and from a person to another person through sexual contact [156]. According to the World Health Organisation (WHO) deaths occur in very few cases and the infection is not dangerous to children and adults [158]. Even if this virus in particular is not lethal in most of the cases, it can damage the newborn's brain during pregnancy still, according to the Pan American Health Organization [158].

The symptoms of Zika can be related to other viral diseases, the main symptoms are red rash, weakness, headaches along with a minor fever and joint pain [159]. Zika is a very specific kind of virus/disease, all infected people do not develop the main symptoms mentioned above. Trends have shown that only one in five people infected by the mosquito will develop the illness [158]. The Zika virus spreads quickly and have had many outbreaks around the world. During 2014-2015 there was a huge outbreak in French Polynesia, a study shows that approximately 11.5% of the whole population sought medical attention with symptoms that matched the symptoms Zika showed. It was later proven that only a fraction of the actual infected sought medical care and had a seroprevalence rate of 49% [160] . During 2016 the first cases of the Zika virus were reported in Brazil and Florida in the US.

In the beginning of 2017 a company called Protein Sciences released that a protein-based vaccine candidate to the Zika virus showed very promising results in the first preclinical trials on animal-based models. The National Institute of Allergy and Infectious Disease sponsored a toxicology test of the vaccine candidate and the result showed that the vaccine had promising safety [161]. The next step is to move on to the human clinical trials to test the effectiveness of the vaccine in the human body compared to the animal body. These human clinical trials were expected to start in the beginning of April, 2017 [162].

This specific vaccine candidate currently under development is as mentioned before a protein-based vaccine which contains a very specific purified protein. This protein called E-protein, has shown to possess the ability to induce a strong immune response in the infected body of a mouse which results in an increased level of antibodies. The E-protein can be found on the surface of the Zika virus [162].

Dengue virus

The Dengue virus (DENV) is also a virus with a long history, the first known infection of the virus were reported during the 1800s [163], since then it has become a real plague in regions with the subtropical and tropical climate around the world. The spreading of Dengue has increased globally over the past few years and almost 40% of the world's population currently lives in countries that are in the risk zone for a Dengue epidemic [164]. According to the WHO it is predicted that approximately 390 million people gets infected by the DENV worldwide each year [165]. The regions that are most vulnerable for epidemics include more than 100 countries throughout the South-East Asia, Western Pacific, Africa, the Americas [165]. There have also been cases of Dengue infection reported in non-subtropical/tropical countries around Europe.

Dengue is as mentioned before also a mosquito-transmitted viral infection. The major difference between the Dengue virus (DENV) and the Zika virus is the fact that Dengue is caused by specific virus with four serotypes (DENV1-4). According to the Centers of Disease Control and Prevention (CDC), the definition of a serotype is as follows: "*a group of microorganisms originating from the same species and sharing distinctive surface structures*" [166].

People infected by the virus are in most of the cases developing symptoms as high fever, headache, joint pain. Dengue can only be spread to humans by mosquitoes and possibly other animals/microorganisms carrying this virus. Unlikely to the Zika, Dengue can not be transmitted between humans, through sexual contact for example [167]. However, the Dengue virus can still be spread from human to mosquito. If a healthy mosquito bites an infected human the virus will be transmitted to the healthy mosquito. The death rate of Dengue is quite low comparing to other diseases such as Malaria. According to the WHO, approximately 2.5% out of 500,000 infected people which develop severe Dengue results in death [168].

A vaccine called Dengvaxia (CYD-TDV) was the first dengue vaccine on the worldwide pharmaceutical market. This vaccine was developed by Sanofi Pasteur and was registred in Mexico during the end of 2015. However, it has been proven that this vaccine only gives the human body a partial protection against the second serotype, DENV2 [163].

There are currently many vaccines candidates in clinical trials, pharmaceutical companies are trying different approaches to develop the ideal vaccine which will give the human body a maximum protection against all of the four serotypes of the Dengue virus. A recent study shows that there are 60 studies of Dengue vaccine in clinical trials. Out of these 60 studies 31 trials in Phase 1, 23 trials in Phase 2 and 6 trials in Phase 3 [169]. Pharmaceutical companies are facing many challenges during the process of developing an ideal Dengue vaccine. The biggest obstacle in the development of the perfect vaccine is that there are currently no animal models that match the human immune response to the virus [170][171]. Animal models including induced DENV into mice have proven to be inefficient, this is because the methods did result in paralysis or death of the used animal.

6. Discussion

This section discusses the results that are considered relevant in each class of biomolecules under separate subheadings. The focus lies in the market and disease trends globally, and in the potential and challenges each market holds.

6.1. Peptide-based Therapeutics

As analysis already predicted, the global peptide therapeutics market value is expected to increase in the next few years. This growth is not only a direct result of the significant increase of approved peptide therapeutics due to the great number of drug candidates in clinical trials and clinical development, but also a result of new strategies in the development of novel, innovative therapeutic peptides. There are currently some successful examples of therapeutic peptides in development that have not only demonstrated an increase in the ability to address intracellular targets, but also an increase in oral bioavailability through these different strategies. When these new properties can be combined with an increased chemical and proteolytic stability – without risking a decrease in bioactivity – therapeutic peptides' already wide range of therapeutic areas can be made even broader and that will revolutionize the pharmaceutical industry.

6.2. Protein-based Therapeutics

The market for protein based therapeutics is on the rise as they are for other biologic based therapeutics. As our lifestyles changes in a more digitalised world with less active lives and with bad diets, obesity is one of the leading causes to disease such as diabetes. The increase

is not only in the west world but also in countries with rising economies such as India and China. Pharmaceutical companies such as Novo nordisk are investing in protein based therapeutics which helps to treat and cure different type of diseases, at the moment they have four types of protein and peptide based therapeutics in pipeline.

Monoclonal Antibodies

As can be seen in Figure 7, the estimated annual sales for 2020 for Humira®, Remicade® and Enbrel® are either lower or on the same level as the reported sales for 2016. One of the main reason for this trend is the market opening for *biosimilars* – biological products that are highly similar to other biological products that has already been approved for use. The high growth rate of the antibody drug conjugates – compared to mAbs – is caused by the global sales of the recently approved drugs Adcetris and Kadcyla® and the large number of drugs in pipeline. The rising number of cancer incidences and increasing investment from the government are also vital reasons for the market growth.

6.3. Carbohydrate-based Therapeutics

The carbohydrate-based therapeutics market is as mentioned earlier at its infancy and there is plenty of room for development. There is much ongoing research in this medical field along with huge investments in current and future projects. The research has been going on for a while and there are still very few carbohydrate-based drugs on the pharmaceutical market — except for the Heparins. The inefficient development of the carbohydrate-based drugs can be explained by their structure.

Carbohydrates are biomolecules with a high polarity which causes problems with the pharmaceutical interaction. A high polarity in a molecule's structure in general results in a problem with the absorption by the human body. The absorption will decrease which will lead to an inefficient drug with low pharmaceutical potential. This is because the drug can't interact with the target and reach its maximal potential due to the bad absorption. The main research on carbohydrate-based therapeutics focuses on the polarity in the structure, the main goal is to synthesize a molecule with a low polarity but still with the characteristics of a carbohydrate. By achieving a molecule with the desired characteristics, a possibility for a good absorption becomes reality. A good absorption in this case will result in a predicted interaction between the drug and the target, a drug with high pharmaceutical potential.

The development of a carbohydrate-based drug will open new doors for treatment of lethal diseases in both the present time and in the near future. This is due to the specific characteristics of the carbohydrates. According to research in general, it is predicted this group will have a huge potential to cure various types of diseases. If this prediction would become a reality in the near future it could change today's treatment of diseases and hopefully cure patients with a resistance to the existing drugs. By having the possibility to cure diseases with carbohydrate-based drugs it will probably lower the risks of eventual side effects caused by the treatment. This is due to the biological properties of the drug which are

human-friendly. Lowered risks of side effects will increase the quality of life, this will result in a healthier society where the patient will not be hampered by the side effects that affects the patient's everyday life.

Even if this market is in particular small compared to the other therapeutical markets it still has one of the oldest biological drugs, the Heparins. This pharmaceutical drug has a over 100 years history and is still a key player on the therapeutical market for anticoagulants. The world's population is facing a dramatic development of thromboembolic disorders. Trends are showing that these disorders have increased drastically and today it is more likely to die from a blood clot than from various types of cancer. These trends are tragic and the reasons for development of this kind of disorders can be many. There are many crucial factors involved in the development of blood clots, one of the major factors has to be stress.

People are living in constant stress today in comparison to the 1900s. The stressful lifestyle is unhealthy for the human body, it affects both the mental state of the human being as much as the organs and the biological function. There is no time to eat properly which results in choosing fast foods over healthy homemade meals. Fast foods contain an increased amount of unhealthy lipids that can have an impact on the development of these disorders. This along with lack of sleep and drinking beverages such as coffee and energy drinks in higher doses. If people will not adjust their lifestyles the consequences can be tragic.

Approximately 800,000 deaths occur annually in Europe and in the US caused by DVT. The majority of these countries are industrial countries with good economies and health care systems. Just imagine how the situation is in the developing countries around the world, where the standard of the healthcare systems are significantly lower compared to the industrial countries. The number of deaths will probably increase even more in Europe and in the US if measures are not taken within the near future.

The observed trends in development of thromboembolic disorders results in more people seeking medical care, which in turn increases the demand for carbohydrate-based heparins. An increased demand for pharmaceuticals results in a higher valued market. This can possibly be the reason why the Heparin market is predicted to increase in value in Europe and almost double globally until the beginning of 2020s. This is good news for the pharmaceutical companies but here comes the next controversy, will the drugs still keep the same high standard?

As mentioned before many continents have lower standards when it comes to the production of pharmaceuticals. The patents for the different subgroups of Heparin have expired which opens the for biosimilars. This possibility will open new doors for pharmaceutical companies around the world which may lead to various outcomes. A pharmaceutical produced with lower standards can result in a tragic outcome. Production in lower standards can mean a lot of things. The purification process during the production can leave residues which can be

toxic to the human bod, the doses of the active substance can differ along with the quality of the active substance. The near future will show how affected the world's population will be by both the tendency to develop various disorders such as new heparin biosimilars.

6.4. Oligonucleotide-based Therapeutics

Considering the history and the development of oligonucleotide-based therapeutics it is clear that this new generation of biomolecules contributes to the bright future of biologics. Throughout the years, the withdrawal of fomivirsen, the decreasing market sales of pegaptanib, the poor marketing of mipomersen and the fact that mipomersen failed to get regulatory approval in the EU has resulted in a downfall on the oligonucleotide therapeutics market. However, the recent FDA approval of nusinersen and eteplirsen – where both drugs are first therapeutical options for SMA and DMD, respectively – indicates that the market is regaining its value. The development of siRNAs and GalNac/lipophilic conjugates in the late 2010s do not only grant great hope for the ON market, but also for patients suffering of hepatitis B virus. The improving targeting strategies, delivery inside the cell/tissue, specificity, technology and further understanding on a cellular and molecular level has resulted in increased number of drugs in clinical development.

As can be observed in Figure 8. the oligonucleotide therapeutics market and investments in the medical field are currently increasing. A greater number of therapeutical drugs in clinical development for one specific disease will increase the possibility to find a treatment option. This trend will hopefully result in multiple new drugs on the market, especially for orphan diseases. If nusinersen succeeds in gaining approval in the EU, doors for new market opportunities will open. The future of oligonucleotide-based therapeutics lie on several factors – will more siRNA conjugates reach clinical maturity and get approval in the US/EU? Will nusinersen get regulatory approval in Europe? What will the outcome of the clinical studies be? These are just few of the challenges this market has to overcome. If the outcome is positive, there is no doubt that the oligonucleotide-based therapeutics market and shares will increase significantly in the future.

6.5. Medical devices

The market for medical devices are predicted to grow in the coming years, see figure 10. Even though the prediction is for 2019, the signs looking at other markets in medical devices, the trend for following years until 2025 the market for medical devices seems to increase overall. The most important products are the combinational ones, which are needed for smarter and quicker ways to treat and cure disease. The market for drug delivery systems is predicted to be one of the largest and most important segment of the medical device market. The main reason is great share of research and capital investments is put into this market. Although combined with nanotechnology, the unknown effects of nanoparticles and the FDA's lack of direct guidelines regarding nanotechnology, can and is hampering the growth

of the market; this could be a bottleneck in the market. Two other large market are the surface coating and antimicrobial surface coating market; both are reaching US$1.3 and US$1.17 billion dollars respectively. The reason for these large markets and their rising is because of the increased activity on stem cell research and demands for products like vaccines, proteins and antibodies, thus also the high demand and need for complication free implants and healthcare. Every year millions of patients are acquiring infections when submitted to hospitals and around 5 % results in death. A smaller but rising market is the market for 3D-printing; pharmaceutical companies are forced to collaborating with medical device companies that for example specialises in 3D-printing because the need to reinvent and to be on the leading edge is a must for pharmaceutical companies due to the rarity of blockbuster drugs as the market for biosimilars are rising.

Lipid based drug delivery

Oncology is the leading application according to the diagram in page 31 "Top 10 Therapy Areas in 2022, Market Share & Sales Growth" (EvaluatePharma® World Preview 2016, Outlook to 2022 artikel). Lipids as drug delivery are a promising concept to enhance a therapeutic efficacy in this application. The current popular up-to-date example is delivery of an oligonucleotide that inhibits and kills tumour cells using lipids as delivery system. Both biologics are relatively new in the pharmaceutical industry and promising improvements are coming. Further pharmaceuticals are expected to be found in the market the following years as many corporations are paying attention to lipids.

The properties of lipids push corporation to drive investments and develop therapeutics with lipids in a variety of forms. The lipids are even used as active substance in the case of LT-02 and not only as delivery systems.

No concrete market values for specific applications could be found for the lipid nanoparticles, no more than studies in rats with specific compounds. Liposomal as drug delivery system has on the other hand been in the market since 1995. Doxil® is a good example of the growing trend of lipids based pharmaceuticals', this case can be seen as a trend for most pharmaceuticals based on lipids or as delivery systems. It can be seen that traditional cancer drugs – that have serious side effects – will be replaced or modified with lipids as the time passes and a great potential in the oncology market application is to be seen.

6.6. Biological vaccines

Diseases/viruses spread by various animals such as mosquitos are increasing rapidly with many uncontrolled outbreaks around the world. This is a global problem that needs a fast solution. The Zika and Dengue are viruses with a long history and scientists have not been able to develop an ideal vaccine still. There are a few candidates in clinical trials but it is still a long way to go before a vaccine can be presented for the public sector. The first developed

vaccines in general are usually not ideal and maybe not working as desired. Many companies on the vaccine market are only trying to develop a vaccine as fast as possible and make money on it. This without taking factors such as side effects and the effectiveness of the vaccine under consideration.

Vaccines are important to mankind because they can save lives around the world. Diseases transmitted through animals are not always lethal to the human being but they can still affect a person's whole life. The Zika virus for example is not lethal in most of the cases and even if only one of five infected develops symptoms it still is a problem. This is because one of five people may happen to be a pregnant woman. The infection may damage the newborn's brain which in worst case scenario can affect its whole life. Hopefully the vaccine candidate to the Zika virus will have the desired effects.

The virus has now spread to Brazil and the United States, among others, this shows that a properly functioning vaccine is really necessary. The explanation of a spread like this can be the global warming, it is really hard to know for sure why the spreading trends of this virus are like this. If the virus keeps spreading across the US it can cause panic which will affect not only the infected people but the whole population of America. This sort of panic can result in an increasing demand for a vaccine because people often want to have something as a relief. Situations like this can in many cases have a tragic result. Pharmaceutical companies will compete against each other in finding the next cure which may result in not fully developed vaccines that do more harm than good.

The situation considering the Dengue virus is also crucial, approximately 40% of the world's population live in the risk zone for the epidemic. This virus is more lethal than the Zika virus, this can be caused by the four serotypes of DENV. It is in general more difficult to develop an ideal vaccine that have protecting properties for all the various serotypes of Dengue. There is currently a vaccine on the market, however it is not an ideal vaccine. Just imagine if a multinational outbreak occur and there is no properly functioning vaccine on the market, this will cause panic especially if the severe form of DENV is developed. Infected people may try to escape from the outbreak countries and carry the virus with them to the countries that are considered to be free from the virus. The outcome of a situation like this can result in a worldwide spread that is uncontrolled and almost impossible to stop.

It is important to have many vaccine candidates because this gives more options, if one candidate fails during the clinical trials there are still other candidates that can succeed. There are currently 6 trials in Phase 3 which is quite many and hopefully the majority of these candidates can be approved and move further to Phase 4 (supervision of the drug after market approval). One of the major difficulties in developing a vaccine during a long amount of time is that diseases/viruses have the ability to mutate. A mutation can occur at any time and a ready-made vaccine can then prove to be worthless when released on the market. The next few months and years will show how the market for biological vaccines will look like and if

pharmaceutical companies are going to succeed in developing an ideal vaccine to prevent viruses such as Dengue and Zika from spreading worldwide and leaving deaths behind.

6.7. Summary

An overview of the different biomolecule classes are summarized in Table 4.

Table 4. Summary of the market value, CAGR, pipeline, potential and eventual limitations of each class of biologics

Class	Market value	CAGR	Pipeline	Potential	Limitations
Peptides	US$14.1 billions (2011)	N/A	- Metabolic diseases - Oncology	- Peptidomimetics	Intrinsic weaknesses
Proteins	US$172.5 billion (2016)	N/A	- Diabetes - Hemophilia	- Semaglutid - N8-GP - Somapacitan	- Intrinsic weaknesses - Instability - Bioavailability
Monoclonal antibodies	US$85.4 billion (2015)	- mAbs 10% - ADCs 21.8%	- Oncology - Hematology	- Reduced side effects - Large therapeutic window of the ADCs	- Toxicity of the ADCs
Carbohydrates (Heparin)	US$8.2 billion (2014)	5.2% to year 2022	-Thromboembolic disorders - Fewer side effects (LMWH)	- LMWH - UH - Biosimilars	- Synthetical limitations due to the polarity in the structure
Oligonucleotides	Synthesis market worth US$1.33 billion (2016)	Synthesis market: 10.6% to year 2021	- Orphan diseases - Hepatitis B virus	- GalNAc-siRNA (Targeting liver) - First therapeutical drug towards SMA and DMD	- Targeting ability and drug delivery - EMA approval
Lipids (Liposomal doxorubicin, Doxil® and other)	US$814.6 million (2015)	6.2 % to year 2024	- LT-02 (Ulcerative Colitis)	- High specificity of target, tumour cells. - Conjugation to other biomolecules	N/A
Medical devices	US$66 billion (2012)	7.9 % to year 2019	-Nanomedicine: 1,500 patents and 22,000 scientific publications	- Target drug delivery, reduce side effects, - Shortens hospitalization	- Unknown effects of nanotechnology - FDA regulations

7. Conclusions

Based on the presented results, it is clear that the market for biomolecule-based therapeutics and medical devices are predicted to flourish as the new generations of peptides, proteins, oligonucleotides, carbohydrates and lipids increase in both approvals and sales. The fact that scientists have gained a broader comprehension on a molecular level due to the advanced technologies has resulted in biologics reaching clinical maturity. The optimized pharmacokinetic properties, greater specificity, and the increased therapeutic window has led to reduced side effects compared to traditional therapeutical alternatives, such as chemotherapy. This is one of the main reasons why pharmaceutical companies, governments and other major key players invest heavily in the biomolecule-based therapeutics market. The market opportunities for biosimilars are also a vital reason for the growth in this medical field. Due to new development approaches — peptidomimetics — the stability of peptides has shown to increase. This results in a huge market and development potential. The protein therapeutics market is the largest among biologics, and their subgroup — the monoclonal antibody-based therapeutics market — is the fastest growing. With a high growth rate of novel therapeutics in development, the market will continue to expand.

Conjugated monoclonal antibodies (ADCs) and GalNAc conjugates to small interfering RNA are just a few examples of high potential drugs that are expected to increase on the market and in clinical development. Oncology is the dominating therapeutic area, where great success has been observed in both clinical and pre-clinical studies. Lipid conjugates have proven to be efficient in the treatment of tumour cells and the cytotoxic ADCs grant great hope for the biomolecule-based therapeutics market. The market is also expected to grow for established biologics; for example the increasing need of anticoagulants is predicted to double the Heparin market to 2023 and the demand for novel treatment alternatives opens market opportunities for Heparin biosimilars. The biological vaccine market is also predicted to grow together with biologics, as mutated animal-spread diseases increase in number. As the number of approved drugs and blockbusters produced by the pharmaceutical industry decreases, the industry is forced to collaborate with companies producing medical devices in order to develop novel, innovative drugs. Although the market for drug delivery nanotechnology is expected to decline due to the unknown effects of nanoparticles, nanoparticles are still a potential application in drug delivery, such as lipid nanoparticles conjugated to siRNA for targeting the liver.

Financial limitations, such as the restricted access of licence reports regarding market analyses and forecasts, were a major obstacle during this degree project. The authors varying basic knowledge due to different educational backgrounds along with the timeframe for the project limits the entirety of the report. The report does not give a full impression of the

market and trends regarding biologics and can be considered as an overview of the different therapeutical classes. Further research is required for a more accurate insight of the market. A more detailed analysis of disease trends — especially cancer and diabetes — would provide a broader picture of the current market status. Further studies of the currently approved biological drugs would also contribute to a more detailed analysis. More focus should lie on studies regarding drug conjugates and medical devices due to their great future potential and large market shares.

8. References

[1] E. Valeur, S. M. Guéret, H. Adihou, R. Gopalakrishnan, M.Lemurell, H. Waldmann, T. N. Grossman, A. T. Plowright, New Modalities for challenging targets in Drug Discovery, Angew. Chem, Int. Ed. 10.1002/ange.201811914
[2] Government Offices of Sweden, Billion kronor investment in next generation biologics, The Government Offices, Stockholm; Dec 2015, available from: http://www.government.se/press-releases/2015/12/billion-kronor-investment-in-next-generation-biologics/
[3] Läkemedelsverket. Biologiska läkemedel [Internet]. Uppsala: Läkemedelsverket; 2015 [dated/reviewed 2015-04-21]. Available from:
[4] Nelson D, Cox M. Lehninger Principles of Biochemistry. 4th ed. Vol. 2005. New York: W.H. Freeman and Company; page 85
[5] Medical Definition of Proteins [Internet]. MedicineNet. [cited 2017 May 17]. Available from: http://www.medicinenet.com/script/main/art.asp?articlekey=15380
[6] NCI Dictionary of Cancer Terms [Internet]. National Cancer Institute. [cited 2017 May 17]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=46092
[7] Monoclonal Antibodies: List, Types, Side Effects & FDA Uses (Cancer) [Internet]. MedicineNet. [cited 2017 May 17]. Available from: http://www.medicinenet.com/monoclonal_antibodies/article.htm
[8] Smith TB. Introduction to Diagnostic and Therapeutic Monoclonal Antibodies. [cited 2017 May 16]; Available from: http://pharmacyce.unm.edu/nuclear_program/freelessonfiles/Vol17Lesson1.pdf
[9] Amna Adnan. What Are Monoclonal Antibodies - Their Synthesis and Uses [Internet]. [cited 2017 May 16]. Available from: http://www.biotecharticles.com/Genetics-Article/What-Are-Monoclonal-Antibodies-Their-Synthesis-and-Uses-334.html
[10] Funaro A, Horenstein AL, Santoro P, Cinti C, Gregorini A, Malavasi F. Monoclonal antibodies and therapy of human cancers. Biotechnol Adv. 2000 Aug;18(5):385–401.
[11] What are Antibodies? | pdl.com [Internet]. [cited 2017 May 17]. Available from: http://pdl.com/technology-products/what-are-antibodies/
[12] Medical Definition of Carbohydrates [Internet]. MedicineNet. [cited 2017 May 17]. Available from: http://www.medicinenet.com/script/main/art.asp?articlekey=15381
[13] NCI Dictionary of Cancer Terms [Internet]. National Cancer Institute. [cited 2017 May 17]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=488672
[14] What is an Oligonucleotide? [Internet]. News-Medical.net. 2010 [cited 2017 May 17]. Available from: http://www.news-medical.net/life-sciences/What-is-an-Oligonucleotide.aspx
[15] What are Oligonucleotides [Internet]. bioSYNTHESIS. [cited: 2017 April 14]. Available from: http://www.biosyn.com/faq/What-are-Oligonucleotides.aspx

[16] Lipids, defining Lipids [Internet]. [cited: 2017 April 14]. Available from: https://dlc.dcccd.edu/biology1-3/lipids
[17] Structure and Function of Lipids – Video & Lesson Transcript [Internet]. [cited 2017 May 17]. Available from: http://study.com/academy/lesson/structure-and-function-of-lipids.html
[18] Medical devices – Medical Products Agency, Sweden [Internet]. https://lakemedelsverket.se. [cited 2017 May 12]. Available from: https://lakemedelsverket.se/english/product/Medical-devices/
[19] Health C for D and R. FDA Basics – What is a medical device? [Internet]. [cited 2017 May 12]. Available from: https://www.fda.gov/aboutfda/transparency/basics/ucm211822.htm
[20] Health C for D and R. Classify Your Medical Device [Internet]. [cited 2017 May 14]. Available from: https://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/
[21] Narechania Siddharth N, Pethani T, Sheth NR. A REVIEW ON COMPARISON OF REGULATORY REQUIREMENTS TO APPROVED DRUG DEVICE COMBINATION PRODUCTS IN EUROPE AND USA. 2014 [cited 2017 May 12]; Available from: http://www.wjpps.com/download/article/1401724258.pdf
[22] Narechania Siddharth N, Pethani T, Sheth NR. A REVIEW ON COMPARISON OF REGULATORY REQUIREMENTS TO APPROVED DRUG DEVICE COMBINATION PRODUCTS IN EUROPE AND USA. 2014 [cited 2017 May 12]; Available from: http://www.wjpps.com/download/article/1401724258.pdf
[23] DRUG DEVICE MARKET – Joining Forces: Global Markets for Drug-Device Combinations | Articles | drug development and delivery back issues | Drug Development & Delivery [Internet]. [cited 2017 May 10]. Available from: http://drug-dev.com/Main/Back-Issues/DRUG-DEVICE-MARKET-Joining-Forces-Global-Markets-f-1025.aspx
[24] Chu PK, Chen JY, Wang LP, Huang N. Plasma-surface modification of biomaterials. Materials Science and Engineering: R: Reports. 2002 Mar 29;36(5 – 6):143 – 206.
[25] Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: An updated review. Int J Pharm Investig. 2012;2(1):2 – 11.
[26] Wang H-J, Di L, Ren Q-S, Wang J-Y. Applications and Degradation of Proteins Used as Tissue Engineering Materials. Materials. 2009 May 26;2(2):613 – 35.
[27] What is nanomedicine? – Definition from WhatIs.com [Internet]. WhatIs.com. [cited 2017 May 18]. Available from: http://whatis.techtarget.com/definition/nanomedicine
[28] Vlieghe P, Lisowski V, Martinez J, Khrestchatisky M. Synthetic therapeutic peptides: science and market. Drug Discovery Today. 2010 Jan;15(1 – 2):40 – 56.
[29] Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Discovery Today. 2015 Jan;20(1):122 – 8.
[30] Research, Pharmaceutical, Reproductive Health, Peptide, Urology, [Internet]. Ferring Pharmaceuticals. [cited 2017 May 19]. Available from: http://www.ferring-research.com/research-development/research/

[31] Lau JL, Dunn MK. Development Trends for Peptide Therapeutics: Status in 2016. 11th Annual Peptide Therapeutics Symposium; 2016 Oct 27; La Jolla, CA.
[32] Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Discovery Today. 2015 Jan;20(1):122 – 8.
[33] COPAXONE® (glatiramer acetate injection) [Internet]. copaxone.com. [cited 2017 May 15]. Available from: http://ssshare.it/LNBN
[34] Zacks.com. Brokerage Research Digest: Teva Pharmaceutical Industries Ltd. 2017 Apr.
[35] Press Announcements – FDA approves first generic Copaxone to treat multiple sclerosis [Internet]. [cited 2017 May 15]. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm443143.htm
[36] About Us | Sandoz [Internet]. [cited 2017 May 19]. Available from: https://www.sandoz.com/about-us
[37] Victoza (liraglutid) – Läkemedelsverket / Medical Products Agency [Internet]. https://lakemedelsverket.se. [cited 2017 May 15]. Available from: https://lakemedelsverket.se/malgrupp/Halso---sjukvard/Monografier-varderingar/Monografier-Humanlakemedel/Humanlakemedel-Arkiv/Victoza-liraglutid/
[38] Liraglutide > Annual Reports of Global Pharmaceutical Companies > WorldWide Sales [Internet]. PharmaCompass. [cited 2017 May 19]. Available from: https://www.pharmacompass.com/sales-forecast/liraglutide
[39] Drugs@FDA: FDA Approved Drug Products [Internet]. [cited 2017 May 19]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022341
[40] European Medicines Agency – Find medicine – Victoza [Internet]. [cited 2017 May 19]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001026/human_med_001137.jsp&mid=WC0b01ac058001d124
[41] Sandostatin® LAR® (octreotide) | Products | Novartis Oncology [Internet]. [cited 2017 May 15]. Available from: https://www.novartisoncology.com/news/product-portfolio/sandostatin-lar
[42] PharmaCompass. [cited 2017 May 19]. Available from: https://www.pharmacompass.com/sales-forecast/octreotide
[43] Waldmann H, Valeur E, Guéret SM, Adihou H, Gopalakrishnan R, Lemurell M, et al. New Modalities for Challenging Targets in Drug Discovery. Angewandte Chemie International Edition [Internet]. 2017 Feb [cited 2017 May 12]; Available from: http://doi.wiley.com/10.1002/anie.201611914
[44] European Medicines Agency – Find medicine – Signifor [Internet]. [cited 2017 May 19]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002052/human_med_001547.jsp&mid=WC0b01ac058001d124
[45] Drugs@FDA: FDA Approved Drug Products [Internet]. [cited 2017 May 19]. Available from:

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=200677
[46] Signifor® (pasireotide) | Products | Novartis Oncology [Internet]. [cited 2017 May 19]. Available from: https://www.novartisoncology.com/news/product-portfolio/signifor
[47] Drugs@FDA: FDA Approved Drug Products [Internet]. [cited 2017 May 19]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process
[48]European Medicines Agency – Find medicine – Prialt [Internet]. [cited 2017 May 19]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000551/human_med_000989.jsp&mid=WC0b01ac058001d124
[49] Patient | PRIALT® (ziconotide) intrathecal infusion [Internet]. PRIALT. 2014 [cited 2017 May 19]. Available from: http://www.prialt.com/
[50] Duggan P, Tuck K. Bioactive Mimetics of Conotoxins and other Venom Peptides. Toxins. 2015 Oct 16;7(10):4175–98.
[51] Claesson A, Danielsson B, Svensson U. Läkemedelskemi. Upplaga 3. Uppsala: Apotekarsocieteten. 2005
[52] Bayer, Small and large molecules [Internet], Bayer; 2015 [viewed: 2017-04-15] AVailable from:http://pharma.bayer.com/en/innovation-partnering/technologies-and-trends/small-and-large-molecules/
[53] B. T. Smith Introduction to Diagnostic and Therapeutic Monoclonal Antibodies, UNM Collage of Pharmacy, Vol.17 Lesson 1. New Mexico; Nov 2012 http://pharmacyce.unm.edu/nuclear_program/freelessonfiles/Vol17Lesson1.pdf
[54] Liu JKH. The history of monoclonal antibody development – Progress, remaining challenges and future innovations. Annals of Medicine and Surgery. 2014;3(4):113-116. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4284445/
[55] MedicineNet/Ogbru O, Davis CP. Monoclonal Antibodies [Internet]. [Viewed: 2017-04-13]. Available from: http://www.medicinenet.com/monoclonal_antibodies/article.html
[56]Scott A, Allison J, Wolchok J. Monoclonal antibodies in cancer therapy. Cancer Immun. 2012-05-01:1-8. [Viewed: 2017-04-13]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380347/
[57] The American Cancer Society medical and editorial content team. Monoclonal antibodies to treat cancer [Internet]. [Cited date 2017-04-13]. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/monoclonal-antibodies.html
[58] Smith TB. Introduction to Diagnostic and Therapeutic Monoclonal Antibodies. [cited 2017 May 16]; Available from: http://pharmacyce.unm.edu/nuclear_program/freelessonfiles/Vol17Lesson1.pdf
[59] 15 A screening J, Am 2013 at 11:03. Monoclonal Antibodies in Therapeutics – a primer [Internet]. In Scientio, Veritas. 2012 [cited 2017 May 18]. Available from: http://inscientioveritas.org/monoclonal-antibody-therapeutics-a-primer/

[60] When is a Fully Human Antibody Really Fully Human? [Internet]. The Chairman's Blog. [cited 2017 May 18]. Available from: http://www.thechairmansblog.com/mabvax-therapeutics/david-hansen/when-is-a-fully-human-antibody-really-fully-human/
[61] What are Humanized Monoclonal Antibodies? | pdl.com [Internet]. [cited 2017 May 17]. Available from: http://pdl.com/technology-products/what-are-humanized-monoclonal-antibodies/
[62] Chimeric Antibodies [Internet]. G.P.S Raghava. [cited: 2017 April 16]. Available from: http://crdd.osdd.net/raghava/absource/chimeric.html
[63] NCI Dictionary of Cancer Terms [Internet]. National Cancer Institute. [cited 2017 May 18]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=470256
[64] Duvall M, Bradley N, Fiorini RN. A novel platform to produce human monoclonal antibodies. MAbs. 2011;3(2):203 – 8.
[65] Harding FA, Stickler MM, Razo J, DuBridge RB. The immunogenicity of humanized and fully human antibodies. MAbs. 2010;2(3):256 – 65.
[66] Naked mAb [Internet]. GenScript. [cited: 2017 April 20]. Available from: http://www.genscript.com/antibody-drug-discovery-glossary/12240/Naked-mAb
[67] Jadiya S. AN IMPORTANT APPROACH IN "MONOCLONAL ANTIBODIES USE FOR CANCER TREATMENT" [cited 2017 May 17]; Available from: http://www.academia.edu/9849649/AN_IMPORTANT_APPROACH_IN_MONOCLONAL_ANTIBODIES_USE_FOR_CANCER_TREATMENT_
[68] Monoclonal antibodies to treat cancer | American Cancer Society [Internet]. [cited 2017 May 17]. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/monoclonal-antibodies.html
[69] Therapeutic Approaches, Monoclonal Antibodies [Internet]. Healio Learn Immunooncology. [cited: 2017 April 20]. Available from: http://www.healio.com/hematology-oncology/learn-immuno-oncology/therapeutic-approaches/monoclonal-antibodies
[70] 23.02.2.2. Naked Monoclonal Antibodies – Pharmacology in one semester [Internet]. [cited 2017 May 17]. Available from: https://sites.google.com/site/pharmacologyinonesemester/23-an-introduction-to-biologics/23-2-protein-biologics-used-as-drugs/23-2-2-proteins-that-function-through-specific-targeting-activity/23-2-2-2-naked-monoclonal-antibodies
[71] Scott AM, Allison JP, Wolchok JD. Monoclonal antibodies in cancer therapy. Cancer Immun [Internet]. 2012 May 1 [cited 2017 May 17];12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380347/
[72] Leader BB. Protein therapeutics: a summary and pharmacological classification. Nature reviews, drug discovery. 2008/01; 7:21-39 http://link.ub.uu.se.ezproxy.its.uu.se/?sid=Entrez:PubMed&id=pmid:18097458

[73] Bcc Research, Global Market for Bioengineered Protein Drugs Showing Modest Growth. 2017 January; Available from: https://www.bccresearch.com/pressroom/bio/global-market-for-bioengineered-protein-drugs-showing-modest-growth
[74] 29 MP| S, EDT 2016 1:16 pm. What Will Drive Novo Nordisk's Growth in Diabetes and Hemophilia? – Market Realist [Internet]. [cited 2017 April 15]. Available from: http://marketrealist.com/2016/09/late-stage-research-pipeline-may-drive-novo-nordisks-growth-diabetes-haemophilia-segments/
[75] 29 MP| S, EDT 2016 1:16 pm. Understanding Strong Growth Trends in Insulin and Novo Nordisk's Profitability – Market Realist [Internet]. [cited 2017 May 22]. Available from: http://marketrealist.com/2016/09/strong-growth-trends-insulin-market-expected-boost-novo-nordisks-profitability/
[76]-[C]Venkat Narayan KM, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F. Diabetes – a common, growing, serious, costly, and potentially preventable public health problem. Diabetes Research and Clinical Practice. 2000 Oct;50, Supplement 2:S77 – 84.
[77] Grand View Research, Monoclonal Antibodies (mAbs) Market Size Worth $138.6 Billion by 2024, Nov 2016
[78]] J. M. Reichert, Antibodies to watch in 2017, MAbs, 2017 Feb.Mar; 9(2): pages: 167-181
[79] D. M. Ecker, S. D. Jones, H. L. Levine, The therapeutic monoclonal antibody market, MAbs, 2015 Jan-Feb; 7(1): pages: 9-14
[80] Global Antibody Drug Conjugates Market Opportunities, Trends and Forecast by 2022 – Market Research Report 2017, Mar 2017
[81] Looking Ahead to 2020: Global Antibody-Drug Market Prediction, Aug 2015; InPress Media Group. Available from: https://adcreview.com/news/looking-ahead-to-2020-global-antibody-drug-market-prediction/
[82] Antibody-drug conjugates—an emerging class of cancer treatment [Internet]. [cited 2017 May 22]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4815767/
[83] Increased clinical pipeline of antibody drug conjugates (ADC) - Joost Melis [Internet]. [cited 2017 May 22]. Available from: http://www.antibodysociety.org/increased-clinical-pipeline-adcs-2016/
[84] Ricci S, Agus G. One hundred years since the discovery of heparin, not so long ago. The story of a loser. Veins and Lymphatics. 2013 Aug 13;2(2):1.
[85] Carbohydrate-Based Drugs: A Unique Tool in Healthcare [Internet]. Drug Discovery and Development. [cited 2017 April 17]. Available from: https://www.dddmag.com/article/2013/10/carbohydrate-based-drugs-unique-tool-healthcare
[86] Gray E, Mulloy B, Barrowcliffe TW. Heparin and low-molecular-weight heparin. Thrombosis and Haemostasis [Internet]. 2008 Apr 11 [cited 2017 Jun 6]; Available from: http://www.schattauer.de/index.php?id=1214&doi=10.1160/TH08-01-0032
[87] MedicineNet, Medical definition of Thromboembolism [Internet]. [Viewed: 2017-05-06] Available from: http://www.medicinenet.com/script/main/art.asp?articlekey=25032

[88] MedicineNet/Wedro B, Blood Clots [Internet]. [Viewed: 2017-05-06]
Available from:
http://www.medicinenet.com/blood_clots/article.html
[89] Myhivclinic, Thromboembolic Disease [Internet]. [Viewed: 2017-05-06]
Available from:
http://myhivclinic.org/thromboembolic-disease/disease-information-overview/causes
[90] University of Maryland Medical University, Mucopolysaccharides [Internet]. [Viewed: 2017-05-06]. Available from:
http://www.umm.edu/health/medical/ency/articles/mucopolysaccharides
[91] Drugbank, Heparin [Internet]. [Viewed: 2017-05-07]. Available from:
https://www.drugbank.ca/drugs/DB01109
[92] Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. Arterioscler Thromb Vasc Biol. 2001 Jul;21(7):1094–1096.
[93] Thrombosis Adviser Bayer, Heparins [Internet]. [Viewed: 2017-05-07]
Available from: https://www.thrombosisadviser.com/heparins/
[94] Fredholm B B. Basal Farmakologi. 1:1. Lund: Studentlitteratur AB; 2014.
[95] Antithrombin III Deficiency Treatment & Management: Medical Care, Surgical Care, Consultations. 2017 Feb 28; Available from:
http://emedicine.medscape.com/article/954688-treatment?pa=mB%2FS8D9%2B%2F6DFh7be5AGYN98dXyuXeCRhwQJTDWFK8w7bG3ezzz4veTLj7g3m7DvVdpA1j6O%2FfzNTXV4xGEMOnMUpYh9Cqy2pnXDanvdYOKo%3D
[96] Thrombosis Adviser Bayer, The Coagulation Cascade [Internet]. [Viewed: 2017-05-07]. Available from: https://www.thrombosisadviser.com/the-coagulation-cascade/
[97] Abdallah E, El-Shishtawy S, Mosbah O. Safety and efficacy of low molecular weight heparin (enoxaparin sodium) in comparison with standard unfractionated heparin for haemodialysis anticoagulation. African Journal of Nephrology. 2015;18(1):6–11.
[98] Claesson A, Danielsson B, Svensson U. Läkemedelskemi. 3. Stockholm: Apotekarsocieteten; 2005.
[99] Vascular Medicine Angiologist/ Dr Weinberg I, Low Molecular Weight Heparin [Internet]. [Viewed: 2017-05-08]. Available from:
http://www.angiologist.com/thrombosis-section/low-molecular-weight-heparin/
[100] Merli GJ, Groce JB. Pharmacological and clinical differences between low-molecular-weight heparins: implications for prescribing practice and therapeutic interchange. P T. 2010 Feb;35(2):95–105.
[101] Introducing biosimilar LMWH anticoagulants [Internet]. Hospital Pharmacy Europe. [cited 2017 May 16]. Available from:
http://www.hospitalpharmacyeurope.com/biosimilars/introducing-biosimilar-lmwh-anticoagulants
[102] Harenberg J, Cimminiello C, Agnelli G, Di Minno G, Polo Friz H, Prandoni P, et al. Biosimilars of low-molecular-weight heparin products: fostering competition or reducing "biodiversity"? Journal of Thrombosis and Haemostasis. 2016 Mar;14(3):421–426.

[103] Läkemedelsverket. Månadsrapport från CHMP och CMDh (juli 2016) [Internet]. [Viewed: 2017-05-09]. Available from: https://lakemedelsverket.se/Alla-nyheter/NYHETER-2016/Manadsrapport-fran-CHMP-och-CMDh-juli-2016/
[104] European Medicines Agency, Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 18-21 July 2016 [Internet]. [Viewed: 2017-05-09] Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002571.jsp&mid=WC0b01ac058004d5c1
[105] S. K. Membe, E. Nkansah, Low Molecular Weight Heparins versus Unfractionated Heparin for Thromboprophylaxis: A Review of the Cost-Effectiveness, Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). 2009: pages: 1-15
[106] Estrada CA, Mansfield CJ, Heudebert GR. Cost-effectiveness of Low-Molecular-Weight Heparin in the Treatment of Proximal Deep Vein Thrombosis. J Gen Intern Med. 2000 Feb;15(2):108–115.
[107] News Medical, Heparin market in Europe estimated to reach USD 3,148.0 million by 2022 [Internet]. [Viewed: 2017-05-10] Available from: http://www.news-medical.net/news/20150617/Heparin-market-in-Europe-estimated-to-reach-USD-31480-million-by-2022.aspx
[108] Thrombosis Adviser Bayer, Venous Thrombosis [Internet]. [Viewed: 2017-05-10] Available from: https://www.thrombosisadviser.com/venous-thrombosis/
[109] *"Therapeutic Oligonucleotides – Methods and Protocols",* Humana Press, John Goodchild, Worcester State University, Worcester, MA, USA, 2011
[110] A. Khvorova, J.K. Watts, The Chemical Evolution of Oligonucleotide Therapies of Clinical Utility, Nature Biotechnology; 35: pages 238-248, Feb 2017
[111] Arthur A. Levin, Therapeutic Oligonucleotides, N Engl J Med 2017; 376: pages: 86-88, Jan 2017
[112] J. Isaacson, A.Evertts, Rexahn Pharmaceuticals (RNN) Initiation Report, LifeSci Capital, May 2016
[113] Nair JK, Willoughby JLS, Chan A, Charisse K, Alam MR, Wang Q, et al. Multivalent *N* -Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing. Journal of the American Chemical Society. 2014 Dec 10;136(49):16958 – 61.
[114] Lundin KE, Gissberg O, Smith CIE. Oligonucleotide Therapies: The Past and the Present. Human Gene Therapy. 2015 Aug;26(8):475 – 85.
[115] Evers MM, Toonen LJA, van Roon-Mom WMC. Antisense oligonucleotides in therapy for neurodegenerative disorders. Advanced Drug Delivery Reviews. 2015 Jun;87:90 – 103.
[116] Oligonucleotide Synthesis Market Worth 2.20 Billion USD by 2021 [Internet]. [cited 2017 May 15]. Available from: http://www.prnewswire.com/news-releases/oligonucleotide-synthesis-market-worth-220-billion-usd-by-2021-605626916.html

[117] Pharmaceutical Manufacturing/Tredenick, T. Oligonucleotides: Opportunities, Pipeline and Challenges [Internet]. Jun 2016. Available from: http://www.pharmamanufacturing.com/articles/2016/oligonucleotides-opportunities-pipeline-and-challenges/?show=all
[118] Centers of Disease and Health Promotion, Data and Indicators [Internet], Atlanta, USA; 2017. Available from: https://chronicdata.cdc.gov/
[119] Aartsma-Rus A. New Momentum for the Field of Oligonucleotide Therapeutics. Molecular Therapy. 2016 Feb;24(2):193 – 4.
[120] ClinicalTrials, USA; 2017 [viewed: 2017-04-22]. Available from: https://clinicaltrials.gov/
[121] Oblimersen – Wikipedia [Internet]. [cited 2017 May 15]. Available from: https://en.wikipedia.org/wiki/Oblimersen
[122] Genta Incorporated: Private Company Information – Bloomberg [Internet]. [cited 2017 May 15]. Available from: https://www.bloomberg.com/research/stocks/private/snapshot.asp?privcapId=28941
[123] Pipeline – Ionis Pharmaceuticals [Internet]. [cited 2017 May 15]. Available from: http://www.ionispharma.com/pipeline/
[124] MIPOMERSEN SODIUM | Sales | Medicare Prescription Data | PharmaCompass.com [Internet]. [cited 2017 May 15]. Available from: https://www.pharmacompass.com/prescriptions/mipomersen-sodium
[125] BENEFIT CA, PRIOR I. MANAGEMENT OF THE REIMBURSEMENT PROCESS FOR SPINRAZA. [cited 2017 May 16]; Available from: https://www.spinraza-hcp.com/content/dam/commercial/specialty/spinraza/hcp/en_us/pdf/spinraza_readiness.pdf
[126] U.S. FDA Approves Biogen's SPINRAZATM (nusinersen), The First Treatment for Spinal Muscular Atrophy | Biogen Media [Internet]. [cited 2017 May 16]. Available from: http://media.biogen.com/press-release/neurodegenerative-diseases/us-fda-approves-biogens-spinraza-nusinersen-first-treatment
[127] About – Ionis Pharmaceuticals [Internet]. [cited 2017 May 16]. Available from: http://www.ionispharma.com/about/
[128] A new drug developed for patients for TTR amyloidosis | Ionis TTR Rx [Internet]. [cited 2017 May 16]. Available from: http://ttrstudy.com/about-the-drug/
[129] About apoC-III | volanesorsen (formerly ISIS-APOCIII$_{Rx}$) [Internet]. [cited 2017 May 16]. Available from: http://apociii.com/about-isis-apociiix/
[130] T. Michler, A.Kosinska, T. Bunse, M. Heikenwalder, D. Grimm, S. Milstein, at ed. Preclinical study of a combinational RNAi/vaccination therapy as a potential functional cure for chronic hepatitis B, Alnylam Pharmaceuticals, EASL, The international liver congress, 24 Mar 2017 [cited 2017 May 17]
[131] Getts A, Mullahy CM. Highlights of Prescribing information, Care Management. [cited 2017 May 17]; Available from: http://academyccm.org/pdfs/cm_dec_2016_jan_2017.pdf

[132] Press Announcements > FDA grants accelerated approval to first drug for Duchenne muscular dystrophy [Internet]. [cited 2017 May 17]. Available from: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm
[133] The Rise And Fall Of Sarepta's Stock Since Exondys 51 Accelerated Approval | Trading Common Sense [Internet]. [cited 2017 May 17]. Available from: http://tradingcommonsense.com/?p=9200
[134] Eugene W. M. Ng, David T. Shima, Perry Calias, Emmett T. Cunningham, Jr., David R. Guyer, Pegaptanib, a targeted anti-VEGF aptamer for ocular vascular disease : Article : Nature Reviews Drug Discovery [Internet]. [cited 2017 May 17]. Available from: http://www.nature.com/nrd/journal/v5/n2/full/nrd1955.html
[135] Pegaptanib – Wikipedia [Internet]. [cited 2017 May 17]. last edited: 8 May 2017 Available from: https://en.wikipedia.org/wiki/Pegaptanib
[136] Biogen Sets $750,000 Initial Price For First-Ever Spinal Atrophy Drug | Xconomy [Internet]. [cited 2017 May 17]. Available from: http://www.xconomy.com/boston/2016/12/28/biogen-sets-750000-initial-price-for-first-ever-spinal-atrophy-drug/#
[137] Puri A, Loomis K, Smith B, Lee J-H, Yavlovich A, Heldman E, et al. Lipid-Based Nanoparticles as Pharmaceutical Drug Carriers: From Concepts to Clinic. Crit Rev Ther Drug Carrier Syst. 2009;26(6):523 – 80.
[138] Purohit DK. Nano-lipid carriers for topical application: Current scenario. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm [Internet]. 2016 [cited 2017 May 18];10(1). Available from: http://www.asiapharmaceutics.info/index.php/ajp/article/view/544
[139] Nanostructured Lipid Carriers: A Novel Platform for Chemotherapeutics. – PubMed – NCBI [Internet]. [cited 2017 May 22]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26279117
[140] Winkler J. Oligonucleotide conjugates for therapeutic applications. Ther Deliv. 2013 Jul;4(7):791 – 809.
[141] Doxil – Drug Information – Chemocare [Internet]. [cited 2017 May ?]. Available from: http://chemocare.com/chemotherapy/drug-info/doxi.aspx
[142] Doxorubicin Market Size is Expected to Reach $1.38 Billion by 2024: Grand View Research, Inc. [Internet]. [cited 2017 May 22]. Available from: http://www.prnewswire.com/news-releases/doxorubicin-market-size-is-expected-to-reach-138-billion-by-2024-grand-view-research-inc-602613665.html
[143]Ambisome Uses, Dosage, Side Effects & Warnings [Internet]. Drugs.com. [cited 2017 May 22]. Available from: https://www.drugs.com/ambisome.html
[144] Yang H, Chaudhari P, Zhou Z-Y, Wu EQ, Patel C, Horn DL. Budget impact analysis of liposomal amphotericin B and amphotericin B lipid complex in the treatment of invasive fungal infections in the United States. Appl Health Econ Health Policy. 2014 Feb;12(1):85 – 93.
[145] Dr. G. Keilhauer (Lipid Therapeutics, oct 2012): Conducting a transatlantic phase III clinical registration program in Ulcerative Colitis

[146] UC Drug Market to See Moderate Growth by 2025 [Internet]. Drug Discovery & Development. 2017 [cited 2017 May ?]. Available from: https://www.dddmag.com/article/2017/02/uc-drug-market-see-moderate-growth-2025
[147]Ulcerative colitis market will see moderate growth to $6.58 billion by 2025 as unmet needs persist [Internet]. GlobalData Plc. 2017 [cited 2017 May 22]. Available from: https://www.globaldata.com/ulcerative-colitis-market-will-see-moderate-growth-to-6-58-billion-by-2025-as-unmet-needs-persist-says-globaldata/
[148] US Nanotechnology Drug Delivery Market Forecast to Grow Significantly Through 2016 | News | drug development and delivery current news | Drug Development & Delivery [Internet]. [cited 2017 May 19]. Available from: http://www.drug-dev.com/Main/Current-News/675.aspx
[149]. 3-D Printing Comes of Age | Qmed [Internet]. [cited 2017 May 19]. Available from: http://www.qmed.com/mpmn/medtechpulse/1-3-d-printing-comes-age
[150] Grunewald SJ. 3D Printing Healthcare Market is Expected to Grow by 18% Annually Until 2020 [Internet]. 3DPrint.com | The Voice of 3D Printing / Additive Manufacturing. 2016 [cited 2017 May 15]. Available from: https://3dprint.com/137461/3d-printing-healthcare-market/
[151] Cell Culture Protein Surface Coating Market 2017 by Product Type, Source Type, Geography, Analysis and Forecast To 2021 [Internet]. [cited 2017 May 21]. Available from: http://www.wpsdlocal6.com/story/35250706/cell-culture-protein-surface-coating-market-2017-by-product-type-source-type-geography-analysis-and-forecast-to-2021
[152] Cell Culture Protein Surface Coating Market To Gain From Rising Demand For Biopharmaceutical Products Including Antibodies, Vaccines & Proteins Till 2025: Grand View Research, Inc. [Internet]. [cited 2017 May 19]. Available from: http://www.wpsdlocal6.com/story/35229778/cell-culture-protein-surface-coating-market-to-gain-from-rising-demand-for-biopharmaceutical-products-including-antibodies-vaccines-proteins-till
[153] Mateescu M, Baixe S, Garnier T, Jierry L, Ball V, Haikel Y, et al. Antibacterial Peptide-Based Gel for Prevention of Medical Implanted-Device Infection. PLOS ONE. 2015 Dec;10(12):e0145143.
[154] Business Model Analysis in Antimicrobial Coatings for Medical Devices Key Players – BASF SE Hydromer, PPG Industries, Royal DSM & SCS – Research and Markets [Internet]. 2016 [cited 2017 May 16]. Available from: http://www.businesswire.com/news/home/20160303006273/en/Business-Model-Analysis-Antimicrobial-Coatings-Medical-Devices
[155] Focus on powder coatings – Antimicrobial Coatings for Medical Devices Market to Reach $1.17 bn by 2020, Volume 2016, issue 7;Available from: from:https://doi-org.ezproxy.its.uu.se/10.1016/j.fopow.2016.06.042
[156] Zika Virus – Transmission and Risks [Internet]. CDC. 2014 [cited 2017 May 17]. Available from: https://www.cdc.gov/zika/transmission/index.html
[157] WHO | Zika: the origin and spread of a mosquito-borne virus [Internet]. WHO. [cited 2017 May 17]. Available from: http://www.who.int/bulletin/online_first/16-171082/en/

[158] Bradford A, 1 LSC| A, ET 2016 03:15pm. Zika Virus: Symptoms, Risk, Treatment & Prevention [Internet]. Live Science. [cited 2017 May 17]. Available from: http://www.livescience.com/53510-zika-virus.html
[159] Government of Canada, Diseases and conditions. Symptoms of Zika virus [Internet]. aem. 2016 [cited 2017 May 17]. Available from: https://www.canada.ca/en/public-health/services/diseases/zika-virus/symptoms-zika-virus.html
[160] Aubrey M, Teissier A, Huart M, Merceron S, Vanhomwegen J, Roche C, et al. Zika Virus Seroprevalence, French Polynesia, 2014 – 2015 – Volume 23, Number 4 – April 2017 – Emerging Infectious Disease journal – CDC. [cited 2017 May 17]; Available from: https://wwwnc.cdc.gov/eid/article/23/4/16-1549_article
[161] 13 SS| NR| CN| J, 2017. Protein-based Zika vaccine shows promise in animals [Internet]. CIDRAP. [cited 2017 May 17]. Available from: http://www.cidrap.umn.edu/news-perspective/2017/01/protein-based-zika-vaccine-shows-promise-animals
[162] Protein Based Zika Vaccine Moves Into Clinical Trials| Learn more.... [Internet]. ELISA Kit, antibody, protein blogs | Learn more.... 2017 [cited 2017 May 17]. Available from: https://www.mybiosource.com/learn/protein-sciences-zika-vaccine-moves-phase-1-trials/
[163] Liu Y, Liu J, Cheng G. Vaccines and immunization strategies for dengue prevention. Emerg Microbes Infect. 2016 Jul;5(7):e77.
[164] 24 RR| J, 2012. WHO says 40% of population at risk for dengue fever [Internet]. CIDRAP. [cited 2017 May 17]. Available from: http://www.cidrap.umn.edu/news-perspective/2012/01/who-says-40-population-risk-dengue-fever
[165] WHO | Dengue and severe dengue [Internet]. WHO. [cited 2017 May 17]. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/
[166] Serotypes and the Importance of Serotyping Salmonella [Internet]. CDC, Centers for Disease Control and Prevention. [cited: 2017 May 14]. Available from: https://www.cdc.gov/salmonella/reportspubs/salmonella-atlas/serotyping-importance.html
[167] Dengue Transmission [Internet]. Scitable by nature education. [cited: 2017 May 14]. Available from: https://www.nature.com/scitable/topicpage/dengue-transmission-22399758
[168] WPRO | Dengue [Internet]. WPRO. [cited 2017 May 17]. Available from: http://www.wpro.who.int/mediacentre/factsheets/fs_09032012_Dengue/en/
[169] Marimuthu P, Ravinder JR. Trends in clinical trials of dengue vaccine. Perspect Clin Res. 2016;7(4):161 – 4.
[170] Zompi S, Harris E. Animal Models of Dengue Virus Infection. Viruses. 2012 Jan 9;4(1):62 – 82.
[171] Zellweger RM, Shresta S. Mouse Models to Study Dengue Virus Immunology and Pathogenesis. Front Immunol [Internet]. 2014 Apr 10 [cited 2017 May 17];5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3989707/