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CURRENT ISSUES REGARDING APPROVED PEPTIDE AND PROTEIN DRUGS IN BULGARIA

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ABSTRACT

Peptide drugs have received a considerable amount of attention by various researchers over last years. Innovations in the health and pharmaceutical sectors are interpreted as a transformation of the potential scientific and technical progress into a real one, by creating new medical products and health services. The development of peptide products is associated with the achievement of both good business results and provision of new products for more efficient treatment and better therapeutic status.

KEYWORDS: Peptides, pharmaceutical market, FDA, EMA, BDA.

The higher healthcare costs pose a new challenge for health authorities and regulatory authorities: identification of the pharmacoeconomic advantages of different diagnostic and treatment methods.[22]

The emergence of alternative therapeutic approaches, the large quantity of new and expensive medical technologies and medications increase the cost of medical services, while limited finances are being spent on healthcare.

Peptides perform various functions in the human organism: they are biologically active hormones, neurotransmitters and neuromediators, growth factors, signal molecules and antibiotics.[2] Since the introduction of the first therapeutic recombinant protein, human insulin[6], proteins have emerged as a major new class of therapeutic agents. The reduced

number of approved drugs produced by the pharmaceutical industry, accompanied by increased R&D costs, requires alternative approaches to increase cost-effective production. All this leads to renewed interest in peptides as potential drug candidates.

The discovery of new peptide-based drugs can help address the existing therapeutic challenges.[8] Diseases that affect the CNS are a therapeutic area with a huge potential for the development of therapeutic peptides[15] In order to maintain cerebral homeostasis, the blood-brain barrier (BBB) strictly regulates the movement of nutrients and metabolites between the blood and the CNS[3] This restrictive diffusion barrier is the major obstacle to the development of CNS agents and impedes the development of new pharmacological agents for the treatment of neurological diseases and pain management. Approximately 98% of the systemically administered small molecules have a limited ability to reach the brain tissue at therapeutic concentrations.[14;5] Almost all large molecules, including peptides, enzymes, monoclonal antibodies, recombinant proteins, are unable to pass through the BBB.[13;4]

There are three major methods to produce therapeutic peptides, the main criterion in selecting the most appropriate ones being the molecular weight of the desired peptide:

- bioactive peptides, produced from plants, animals or humans (derived from naturally occurring peptide hormones or larger proteins fragments);
- peptides, isolated by genetic or recombinant DNA methods;
- peptides, obtained through a chemical synthesis.[7] With the inclusion of non-proteinogenic amino acids and pseudopeptide linkages, chemical synthesis allows the production of a large number of peptide derivatives with various effects.[10]

Key companies in this industry are: Eli Lilly and Co; Pfizer Inc; Amgen Inc.; Takeda Pharmaceutical Company Limited; Teva Pharmaceuticals Industries Ltd; Lonza Inc.; Sanofi; Bristol-Myers Squibb; Astra Zeneca PLC; Glaxo Smith Kline PLC; Novartis AG; Novo Nordisk A/S; Bachem Holding AG, PolyPeptide Group Inc.

Market Value and Forecast

The world market for therapeutic peptides is growing almost twice as fast as the market for all other pharmaceuticals.[10] The "Global Peptide Therapeutics Market & Clinical Trials Insight 2022" was published in May 2017 and presents various clinical and non-clinical issues related to the development of the global market for peptide drugs. According to this report, 688 peptide molecules are in different stages of clinical trials and more than 100

peptide drugs are already in use.[20] In 2016, the global market for therapeutic peptides was estimated at 21.5 billion dollars, with expectations of 9.4% increase by 2025[17] with a major predominance in innovative peptide drugs.

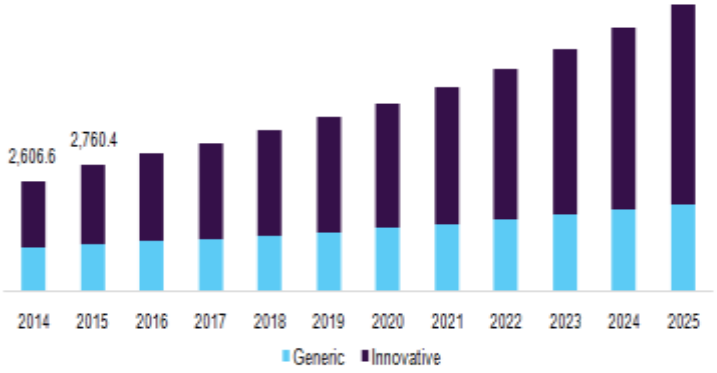


Fig. 1: The therapeutic peptides market according to the type of the drug molecules.[17]

According to the analyst company IMS Health, the increased sales of medicines in Bulgaria in 2015 are due to the growth of several classes of original drugs: antineoplastic, biological and new antidiabetic agents – groups, where there are innovations. The generic market is growing in the standard classes, mostly in the field of cardiology.[19] IMS Health forecast states that in 2020 in Bulgaria, 55% of the cost of medicines will be for original drugs, 30% for generics and 15% for OTC drugs. Medication costs will increase by approximately 30% over the next five years, the main reason being the increased access to treatment for patients with chronic illnesses and introduction of new therapies.[23]

Over the years, the main problems of the pharmaceutical sector in Bulgaria remain the low budgets of health institutions, their mismanagement and the low reimbursement level. With a market of BGN 2.6 billion, the treatment in hospitals paid by the health insurance fund is about BGN 1.4 billion, and patients themselves pay BGN 1.2 billion, which is the highest level in the EU. The policy of rational spending of limited financial resources should be oriented so that the treatment with generic medicines leads to cost savings to be used to pay for expensive new drugs without analogy or alternative.[21]

Factors determining the growth of the global market

- economic factors, such as government policies for start-ups in emerging economies, increase in direct foreign investment in emerging regions and increased health care costs;
- increased number of patients diagnosed, with oncological diseases and increased prescription of peptide therapeutic agents;
- increased awareness among patients and healthcare professionals about the adverse effects of chemotherapy and radiotherapy, which is a prerequisite for increased interest in alternative therapies;
- rapidly growing number of metabolic disorders (osteoporosis, obesity, diabetes) due to increased geriatric population, sedentary lifestyle, unhealthy eating habits;
- intensive development and research for effective and rapid therapeutic agents by research teams.[17]

Peptide drugs have a high level of safety and efficacy and are therefore widely accepted among medical professionals and patients. In clinical practice they are used for the treatment of diabetes, neoplastic diseases, infectious diseases, cardiovascular diseases and others.[18]

AIM

The study was conducted in the following directions: to investigate the market of registered peptide drugs in the United States, Europe, and Bulgaria in particular, their distribution by therapeutic classes and an analysis of the disadvantages and advantages of their wider introduction into the therapeutic practice.

MATERIALS AND METHODS

Information from Bulgarian and foreign literary sources (including articles, publications and a database on peptide drugs) was summarized and analyzed using **content analysis.** Using the data from THPdb, EMA, Ministry of Health (MH) - BG, we studied what amount of the FDA-registered peptide drugs are licensed for use in the EU and Bulgaria. Using a comparative analysis of existing data and based on literary sources, we performed a SWOT analysis of this new therapeutic class of drugs. The data for the medicines registered in Bulgaria are taken from the registers of the National Council on Prices and Reimbursement of Medicinal Products as of 02.02.2018.

RESULTS AND DISCUSSION

THPdb[16] is a comprehensive database containing information on 239 US-FDA approved peptide and protein molecules and their 380 drug variants, classified by Leader et al.[9] in four categories (Fig. 2).

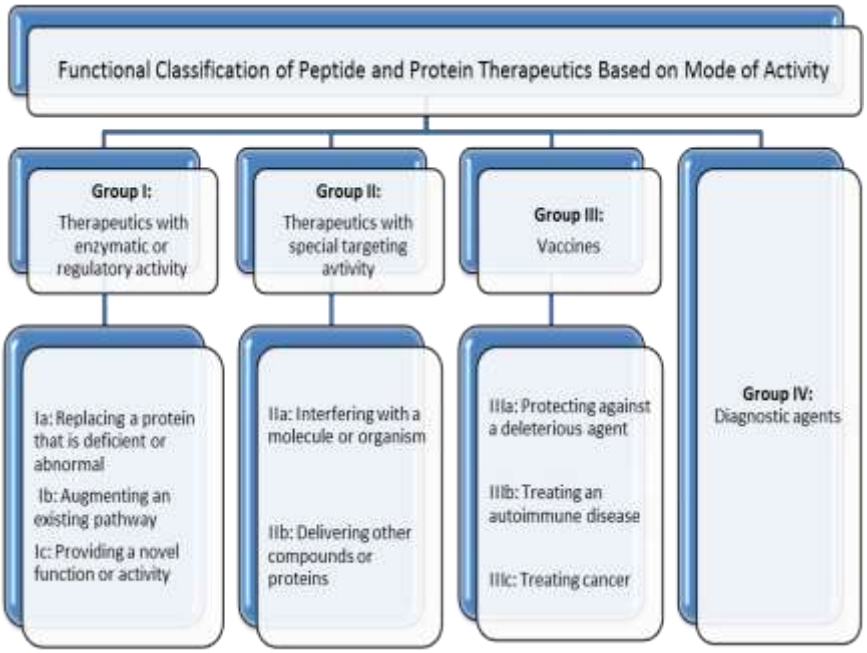


Fig.2. Classification of therapeutic peptides and proteins, according to the mechanism of action and activity *(*Adapted from THPdb: Database of FDA-approved peptide and protein therapeutics, 2017).

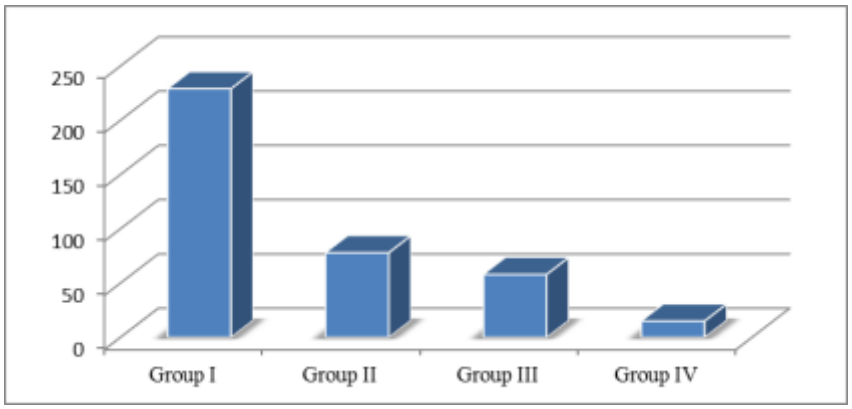


Fig.3. Distribution of peptide drugs based on the classification by Leader et al., 2008.

Figure 3 shows the distribution of US-FDA-registered peptide drugs. The largest number of the drugs (229) are in Group I - proteins with enzymatic or regulatory activity. They are divided into three subcategories: Ia - replacing a missing or abnormal protein; Ib –

augmenting an existing pathway; Ic - providing a novel function or activity. The number of the drugs in Group II (with a special targeting activity) is 78. They are divided into two subgroups: IIa – peptides, interacting with a particular molecule; IIb – peptides, acting as transport molecules supplying other compounds. Group III (vaccines) includes 58 peptide drugs. IIIa – vaccines, protecting against harmful effects; IIIb – vaccines, treating autoimmune diseases; IIIc - vaccines, used in oncological diseases. Group IV consists of 15 drugs used as diagnostic agents.

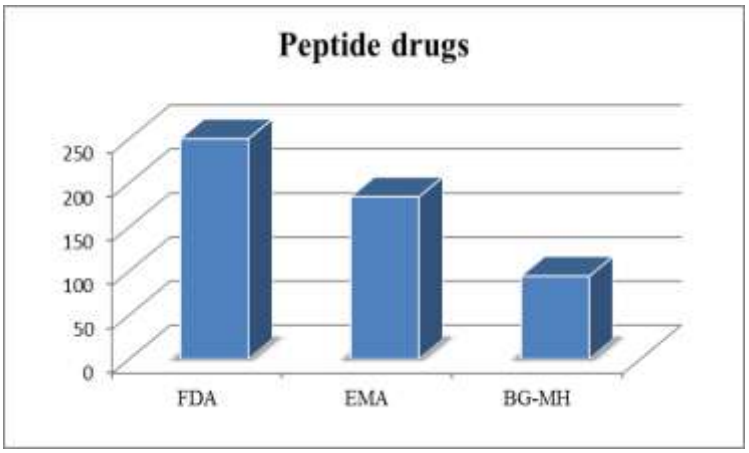
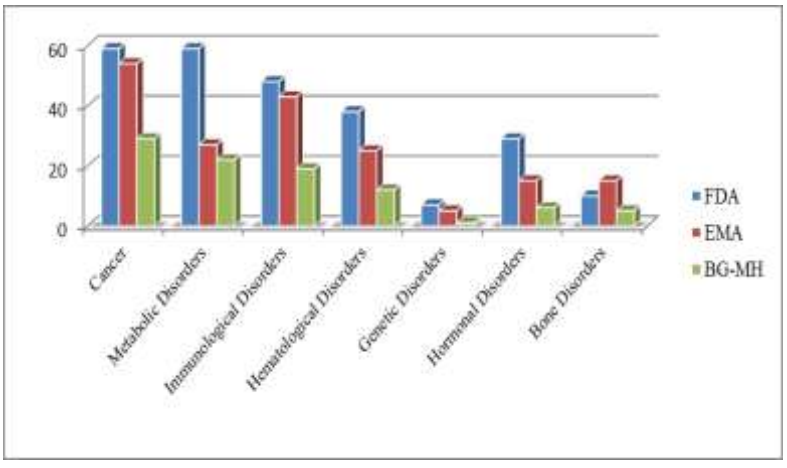


Fig.4. Total number of registered peptide drugs.

Figure 4 shows the total number of registered peptide drugs from FDA, EMA and Ministry of Health (MH) - BG. It is evident that the number of registered drugs in Bulgaria is twice as less than in the EU and about 3 times less than in the USA. The number of registered drugs in the THPdb database is higher, because some peptide and protein molecules are prescribed for various diseases. The incorporation of one therapeutic molecule for various medical indications leads to higher market penetration.



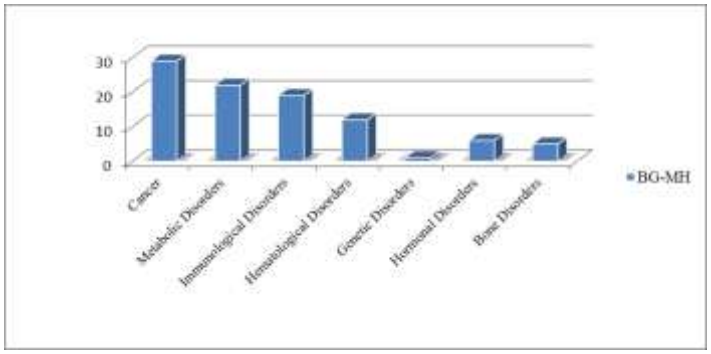


Fig.5. Distribution of peptide drugs by disease.

According to THPdb, the greatest number of peptide drugs is in metabolic disorders (89) and immunology (80), followed by haematological diseases (74), hormonal disorders (63) and neoplastic diseases (61). There are 46 registered drugs for genetic diseases, 35 for infectious diseases, 14 for cardiovascular diseases, 10 for bone diseases. As we can see from Figure 5, the largest number of registered drugs in Bulgaria is for the treatment of neoplastic diseases - 29. The registered peptide drugs for metabolic disorders are 22 and for immunological diseases - 19.

There are 7 drug products in the FDA registry used in neurological disorders: 5 of them are registered in Bulgaria and 3 in the EU. There are 6 respiratory diseases drugs registered in the FDA. From these, Poractantalfa (Curosurf) was registered as a lung surfactant in Bulgaria, and Mepolizumab (Nucala), with antineoplastic and immunomodulating effects, was registered in EMA and in Bulgaria.

Figure 6 shows the distribution of drugs according to the route of administration. Currently, most of the peptide drugs are administered parenterally – 92% (i.v. – 158, subcutaneous – 116, i.m. – 49). The number of peroral drugs is only 13 (4%), e.g. Cyclosporine (Neoral™) and Desmopressin (Minirin™).

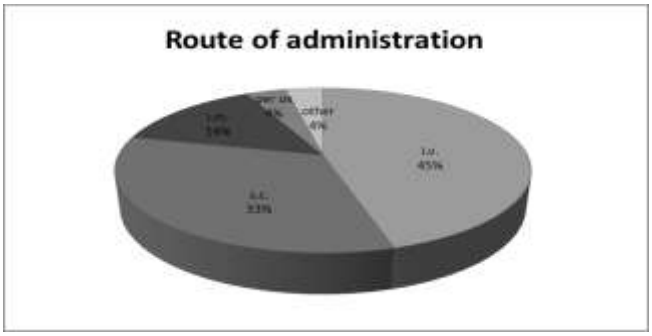


Fig.6. Distribution of peptide drugs according to route of administration (Adapted from THPdb: Database of FDA-approved peptide and protein therapeutics, 2017)

SWOT – analysis

Strengths	**Weaknesses**
Good efficacy, safety and tolerability High selectivity and low levels of toxicity Predictable metabolism Quick release on the market Standard synthesis protocols	Chemically and physically unstable Tendency to hydrolysis and oxidation Aggregation tendency Short half-life and rapid elimination Limited per os intake (low complience) Low permeability of the cell membrane
Opportunities	**Threats**
Discovery of new peptides Optimized design sequences New ways of administration/application Multifunctional peptides and conjugates with more than one pharmacological activity	Immunogenicity Advances in genomics and personalized medicine A significant number of patent surprises Increased safety and efficacy requirements for novel small molecule drugs

Advantages of peptides relative to other proteins used as drugs

- peptides can more easily penetrate tissues than proteins and antibodies because of their smaller size;
- therapeutic peptides, even synthetic ones, are less immunogenic than recombinant proteins and antibodies (assuming the peptide does not contain an amino acid sequence recognized by the immune system);
- lower production costs (synthetic compared to recombinant);
- higher activity (15-60 times) per unit mass (assuming 75kD per antibody and 10-50 amino acids per therapeutic peptide).[11]

  Therapeutic peptides also have several advantages over small organic molecules, such as traditional drugs.
- peptides possess higher efficacy, selectivity and specificity, e.g. in most cases they are an analogue to the functionally active fragment of the protein;
- peptide degradation products are amino acids, which reduces the risk of systemic toxicity and minimization of drug interactions;
- their short half-life prevents accumulation in tissues, which reduces the risk of complications caused by their metabolites.[12]

CONCLUSION

Peptides are considered poor drug candidates because of their high molecular weight, low lipophilicity and the presence of charged functional groups, which prevents their absorption in the gastrointestinal tract (GI tract). Following oral administration, the peptides undergo rapid enzymatic degradation and reduced blood absorption, resulting in low bioavailability

and rapid metabolism.[1] In order to improve the pharmacokinetic parameters such as the volume of distribution (Vd), clearance (CL) and bioavailability (AUC), variations of existing drug molecules are produced.

The future development of peptide drugs will continue to build on the strengths of naturally occurring peptides with the application of traditional rational design to improve some of their shortcomings (e.g. physical and chemical properties). New peptide synthesis technologies enable the production of various molecules, including multifunctional peptides, cell-penetrating peptides and peptide drug conjugates, which will extend the therapeutic areas of application. In the future, the number of intradermally and nasally administered peptides is expected to increase by more than 14%, since these administration routes avoid enzyme degradation. It has also been estimated that the bioavailability of nasally administered peptides is over 4%, which is another advantage over the oral route.[16] Peptides have a tremendous potential for development as a future therapy for the treatment of unmet medical needs.

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