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Review article

Features of the Patent Researches of Nanotechnology-Based Drug Development

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The aim of this study was to analyze features of thepatent researches of nanotechnology-based drug development. It has offered the algorithm of thepatent researches, which takes into account thesearchin patentdatabasesand scientificresources, the use of the InternationalPatent Classification, the European Classification, the United States Patent Classification and specifickeywords, top pharmaceutical company namesin the nanotechnology field. It has found out active patenting of nanoparticles as the pharmacologically active substances and their technologies, nanoparticles for drug delivery. It has established that nanotechnology has used for the drug developments of most pharmaceutical groups. Studies suggest perspective and advantage use of nanotechnology in the drug development in the form of nanoparticles, as well as nanocontainers with high pharmacological activity, bioavailability and safety.

Key words: Nanotechnology, Drug, Patent research.

Nanoteknoloji Esaslı İlaç Geliştirme Patent Araştırmalarının Özellikleri

Bu çalışmanın amacı, nanoteknoloji esaslı ilaç geliştirme patent araştırmalarının özelliklerini analiz etmekti. Bu, patent veritabanlarında ve bilimsel kaynaklarda, Uluslararası Patent Sınıflandırması'nın kullanımında, Avrupa Sınıflandırması'nda, Birleşik Devletler Patent Sınıflandırması'nda ve spesifik anahtar kelimeleri, nanoteknoloji alanında üst ilaç firmalarının isimlerini içine alan patent araştırmalarının algoritmasını sağladı. İlaç geliştirmede nanopartiküller, farmakolojik olarak etkin madde şeklindeki nanopartiküller ve teknolojilerinin aktif patentlenmeleri ortaya çıkarıldı. Pekçok farmasötik grubun ilaç geliştirmesinde nanoteknolojinin kullanıldığı tesbit edildi. Çalışmalar, yüksek farmakolojik aktivite, biyoyararlanım ve güvenlikle nanopartiküller ve yanısıra nanotaşıyıcılar formunda ilaç geliştirmede nanoteknoloji kullanımının avantaj ve perspektifini gösterdi.

Anahtar kelimeler: Nanoteknoloji, İlaç, Patent araştırması

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INTRODUCTION

Currently all over the world nanotechnologies are widely recognized, and thanks to its practical potential are considered one of the most promising areas, and the effect of their use in social and economic spheres must be significant. One of the most significant members of nanotechnologies is the pharmaceutical industry. Among the promising areas of nanotechnology-based drug discovery scientists point out use of molecules as active substances; development of delivery systems for active drug substances to organs and target cells. It has established considerable advantages of nano-drug delivery system from the perspective of greater clinical efficacy, reducing toxicity and the risk of side effects, the feasibility of a controlled or sustained release of the active ingredient, as well as the possibility of targeting it to the affected organ or tissue (1, 2).

Status, structure, dynamics, trends and prospects of nanotechnology-based drug developments require continuous monitoring of information. Pharmaceutical companies running in the nanomedicine compete with each other, carry out an analysis of own competitive position and the position of competitors. Study of patent activity is important for the assessment of the innovative capacity of the organization, the industry, the country. Properly conducted patent researches can not only provide a high technical level and competitiveness of products, but also reduce the cost of its creation by eliminating the duplication of research and development. Conducting of patent researches is an obligatory stage R&D for all businesses.

Features of patent researches in nanotechnology are the subject of many domestic and foreign scientists. There are the following reasons for the complexity of finding relevant technical solutions relating to the nanotechnology-based objects (3, 4):

-the uncertainty of understanding and classification of technical character of inventions to the nanotechnology-based objects;

-a greater degree of scattering of patent documents in the International Patent Classification (IPC);

-the absence of an elaborate classification scheme for a class B82 “Nanotechnology”;

-the lack, with few exceptions, in other places of the IPC close classification, explicitly reflecting the various aspects of nanotechnology;

-different approaches to the classification applied by different patent offices;

-the lack of Russian glossary of terms and keywords, developed for different objects of nanotechnology;

-the need to refer to the translated literature for the selection of keywords for search in foreign databases.

It has shown that the verification of compliance with patentability criteria, analysis of trends, infringement search and competitiveness assessment of developments in nanotechnology field have a number of specific features that require special methodological approaches in conducting a patent search. At the same time, researches related to comprehensive assessment of the features of the patent researches in nanomedicine have not been carried out yet. The aim of this study was to analyze features of the patent researches of nanotechnology-based drug development.

EXPERIMENTAL

Studies were conducted using a database on the Internet: Ukrainian patent office, patent office of the Russian Federation, the European patent office, the US patent office, the Food and drug administration, European Medicines Agency (EMEA), State enterprise “The State Expert Center” of the Ministry of Health of Ukraine. It has used retrospective, logical, systematic and analytical methods.

RESULTS AND DISCUSSION

The analysis has found out that nanotechnology is a multi-industry and multi-disciplinary field, so inventions in the pharmaceutical field can be distributed in different sections of the patent classification. An analysis of patent information is carried out using databases of patent offices, as well as periodicals. A common means of access to the databases of patent offices is the Internet. In addition, the publication approved drug

products with therapeutic equivalence evaluations (the List, commonly known as the Orange Book) is an object of intense interest in the nanomedicine area. In the Orange Book scientists can search information related patenting, registration of active substances, drugs, including nanoparticles or nano-drug delivery system.

It is useful in patent databases to use a number of classification systems: the International Patent Classification, the classification of the European Patent Office (EPO) – ECLA (It is mainly an extension of the International Patent Classification system, but sometimes modifies its titles and rules), the United States Patent Classification (a predominantly functional classification). Common to using of classification headings of the United States Patent Classification and ECLA is that indexing nanosubject heading has never used alone, but only in combination with other headings.

However, if investigators use for searching only patent classification, the rather large array of patent documents will remain unstudied, which could lead to negative consequences, both in the development of patenting as well as in production?

In the pharmaceutical field to improve the accuracy of search for documents it is advisable to use a set of specific keywords (5). In addition, it is necessary conduct name search by top pharmaceutical company names in the nanotechnology field.

In addition to the analysis and systematization of patent documentation patent researches include the study of scientific and technical documentation. The most efficient resources in terms in scientific research in pharmacy are the bases with online access and logical and morphological advanced search capabilities (database of the National Center for Biotechnology Information: PubMed, PubChem, etc.).

The analysis, systematization of literature data has allowed to offer author algorithm of the patent researches of nanotechnology-based drug development (Figure 1).

It should be noted that despite the wide opportunities for innovation in the pharmaceutical field, in modern science there is a problem of risk assessment of nanoparticles for humans and the environment. According to our analysis, there are certain difficulties in identifying the degree of toxicity nanodrugs. Thus, the toxicity of nanoparticles cannot be assessed based on a comparison with analogues in paucidisperse system because toxicological properties of nanomaterials are result not only to their chemical composition, but changing the size and shape of particles and their surface characteristics, chemical reactivity, and others. A significant problem is also insufficient developed methods for detection and quantification of nanoparticles in the environment, food. Conducting of patent researches in nanomedicine it is necessary to consider a number of scientific and regulatory requirements: the accuracy of the assessment methods of interaction of nanosystems with biological systems (effects on the body, the central nervous system, immune system, reproductive function, embryogenesis, etc.), the comparability of existing nanocompositions, the availability of standardized tests to assess the safety of nanoparticles and other (6).

Thus, the potential benefits of the nanodrugs are enormous, but there is uncertainty about the risks of many products nanomedicine, concerns about the adequacy of regulatory pharmacovigilance, uncertainty about the potential risks to the health of patients.

However, today, at the global pharmaceutical market a number of nanodrugs has already registered (7). It has analyzed of patent strategy on the example of foreign pharmaceutical companies that have registered nanodrugs and have been present on the market for over 10 years (Table 1).

As a result of the patent researches it has found out active patenting nanoparticles as the pharmacologically active substances and their technologies, and nanoparticles for drug delivery (liposomes, PEGylated proteins, polypeptides, aptamers, nanocrystals, polymer-based nanoformulations, protein–drug conjugates, surfactant-based nanoformulations, metal-based nanoformulations). The findings indicate the prospects and demand of nanodrugs in the global pharmaceutical market. It should be noted that today nanotechnologies use for the dug development of most pharmaceutical groups. Thus, among the analyzed patents and

applications it has identified agents for alimentary tract and metabolism; medications for blood and blood forming organs; drugs affecting the cardiovascular system, including lipid lowering agents; antimicrobials, antineoplastic and immunomodulatory agents. These drugs help to more effective therapy, prolonging the action, prolonged circulation in the blood, targeted delivery to the target organ, safety.

As known medicinal products based on nanotechnologies are expensive drugs. However, these costs are justified in medical practice, especially in the treatment of diseases such as tuberculosis, AIDS, cancers, prolonging the life of patients and improving their quality of life. Thus, the benefits of nanoliposome anticancer drugs include the possibility of targeting chemotherapeutic substances in the tumor and foci of inflammation, as well as reducing the toxicity of drugs, to increase their safety.

It should be noted major foreign pharmaceutical corporations (Pfizer, GlaxoSmithkline, Merck & Co, AstraZeneca, Squibb Bristol Myers, Hoffmann La Roche etc.) have patented innovations in nanotechnology.

A striking example of active innovation policies in the field of nanotechnology is a tactic of the pharmaceutical company Elan Pharma, which has developed the technology to produce nanocrystals. This company owned patents for the following drugs in nanoparticulate form: olanzapine, fenofibrate, clarithromycin, cyclosporine, corticosteroids (fluticasone, triamcinolone, beclomethasone), antihistamines, bisphosphonates, nimesulide, vaccines, metaxalone, glipizide, griseofulvin, statins, naproxen, protease inhibitor AIDS virus etc.

Patent analysis has revealed that active pharmaceutical researches have conducted in the field of nanotechnologies in Ukraine. Pharmacological studies of nanoparticles of magnesium (patent UA34486), silver (UA95555), phyto-nano- therapy (UA38384, UA38385), anticancer nanocompostion (UA64374), fullerene nanocomposition (UA79893, UA91797), carbon nanotubes (UA92992), a pharmaceutical composition in the form of gel with silver nanoparticles for treatment of wounds and inflammatory infections (UA92307) and others are carried out.

It should be noted that many clinical trials of nanodrugs approved by the FDA have been conducted in recent years. These studies have shown that the use of nanodrugs opens up new possibilities in the treatment of pathologies, providing higher efficiency, reducing the risk of adverse reactions, improving the quality of life of patients (Table 2).

Thus, the studies indicate the prospects and feasibility of nanotechnology-based drug developments in the form of nanoparticles, as well as the nanocontainers with high pharmacological activity, bioavailability and safety. There is no doubt that the success of the creation, production and use such drugs is the presence of an effective system of patent protection.

It should be noted that that nanotechnology is a typical example of oriented basic research. It is necessary not only to maintain and develop these studies themselves, but also to step up the process of transforming their results in intellectual property and intellectual resources of the pharmaceutical companies.

It is possible to identify the following difficulty commercializing drugs in the field of nanotechnology: a long period of launch to market, high technology risks in uncertain benefits at the start of work, the high cost of development and deployment of nanotechnology, the complexity of scaling of laboratory results, the complexity of the legal protection and intellectual property protection (detection of an infringement of the nanotechnology requires expensive research methods). In addition, for applied research is necessary to involve specialists from different disciplines and possess knowledge at different levels of scale (nano, micro and macro) (32-34).

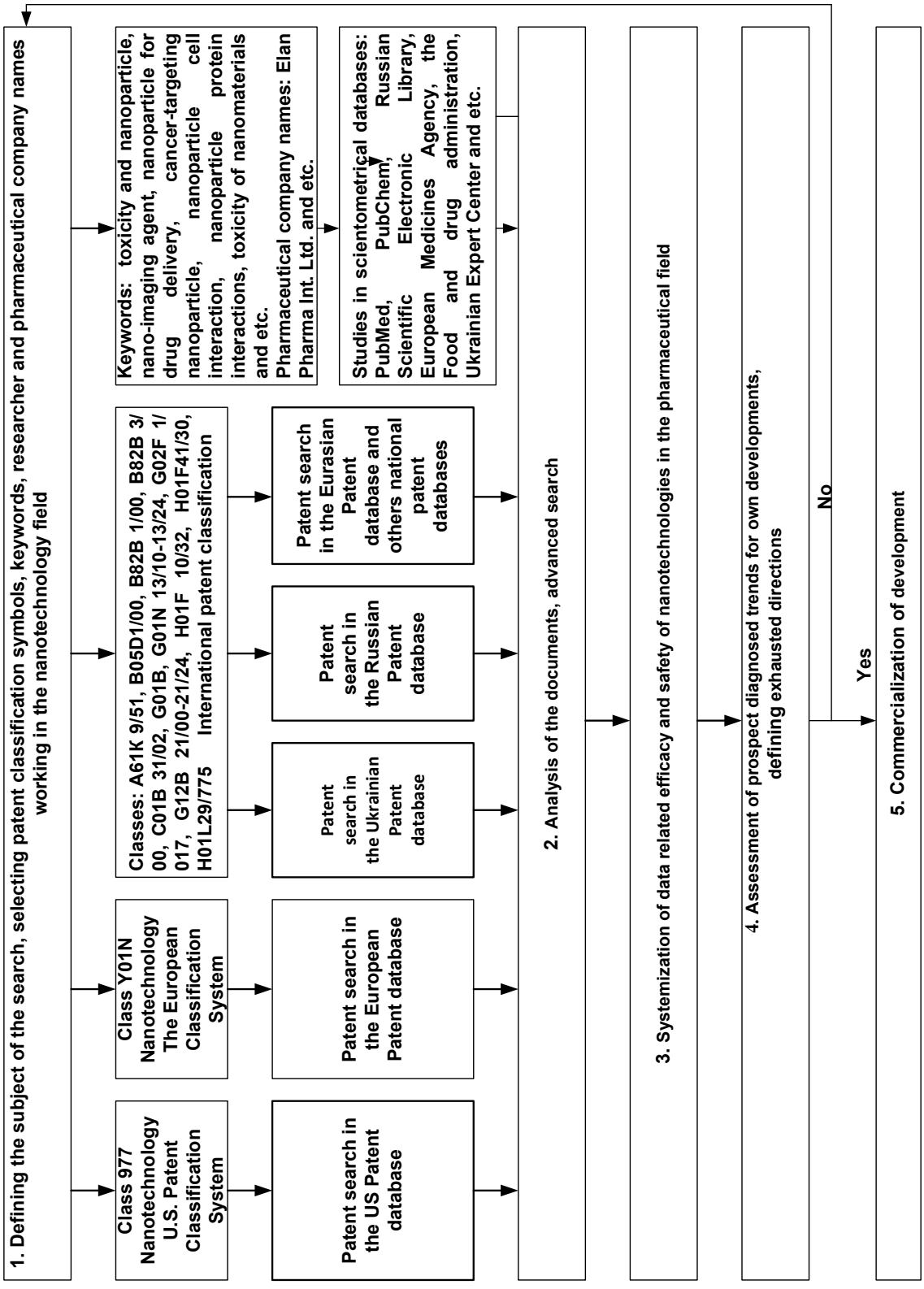

Figure 1. The algorithm of the patent researches of nanotechnology-based drug development

Table 1. Patent protection of registered foreign nanodrugs

No	Trademark, active pharmaceutical ingredient	N US patent; number of corresponding patents	Patent expiration	The anatomical therapeutic chemical classification	Approval FDA	Producer, Country
1	2	3	4	5	6	7
Liposomes						
1	AmBisome; amphotericin B	US5874104 US5965156; 15	23.02.2016 12.10.2016	Antimycotics for systemic use.	1997	Gilead Sciences Inc., US
2	DaunoXome; daunorubicin citrate	US5441745 US5435989 US5019369 US4946683 US4753788; 26	Patents have expired	Antineoplastic agents. Cytotoxic antibiotics and related substances. Anthracyclines and related substances.	1996	Gilead Sciences Inc., Canada , US
3	DepoCyt; cytarabine	US5723147; 21	Patents have expired	Antineoplastic agents. Antimetabolites. Pyrimidine analogues.	1999	Enzon Pharmaceuticals Inc., US
4	DepoDur; morphine sulfate	US5723147 US5807572 US5891467 US5931809 US5962016 US5997899 US6171613 US6193998 US6241999; 21	03.03.2015 15.09.2015 31.01.2017 14.07.2015 31.01.2017 01.09.2016 01.10.2016 01.09.2016 01.09.2016	Analgesics. Opioids. Natural opium alkaloids.	2004	EKR Therapeutics, Bedminster, US
5	Doxil; doxorubicin hydrochloride	US5213804; 54	Patents have expired	Antineoplastic agents. Cytotoxic antibiotics and related substances. Anthracyclines and related substances.	1995	Ortho Biotech, Bridgewater, US
6	Inflexal V; influenza virus antigens	US5879685; 16	Patents have expired	Influenza vaccines.	1997	Berna Biotech, Bern, Switzerland
7	Marqibo; vincristine sulfate	US 6723338 US 7247316 US 7887836; 68	31.03.2020 25.09.2020 31.03.2020	Antineoplastic agents. Vinca alkaloids and analogues.	2012	Talon therap, US
8	Mepact*; mifamurtide	US4971802; 22	Patents have expired	Immunostimulants. For the treatment of high-grade resectable non-metastatic osteosarcoma.	- (Approval Europe 2009)	Takeda, Italy
9	Visudyne; verteporfin	US5707608 US 5756541 US 5770619 US5798349; 31	02.08.2015 11.03.2016 06.06.2015 25.08.2015	Ophthalmologicals. Ocular vascular disorder agents.	2000	QLT Inc.,US, England , Canada

1	2	3	4	5	6	7
Lipid-based (non-liposomal) formulations						
10	Abelcet; amphotericin B	US6406713; 44	18.06.2019	Antimycotics for systemic use.	1995 1996	Enzon Pharmaceuticals Inc., US
PEGylated proteins, polypeptides, aptamer						
11	Oncaspar; PEGylated L-asparaginase	US4179337; 9	Patents have expired	Antineoplastic agents.	1994	Enzon Pharmaceuticals Inc., US
12	Somavert; pegvisomant PEGylated human growth hormone receptor antagonist	US6057292 US5849535; 73	21.09.2015 25.03.2017	Systemic hormonal preparations.	2003	Pharmacia and upjohn, US
13	Macugen**;** PEGylated anti-VEGF aptamer pegaptanib sodium	US5932462 US 6011020 US6051698; 9	03.08.2016 04.07.2017 19.05.2015	Ophthalmologicals. Ocular vascular disorder agents.	2004	Nektar Therapeutics, San Carlos, Canada, US; OSI Pharmaceuticals, Melville, US
Nanocrystals						
14	Emend*; aprepitant as nanocrystal	US 5719147 US 6096742 US8258132; 34	17.04.2015 01.08.2018 26.09.2027	Antiemetics and antinauseants.	2003	Merck Sharp & Dohme Corp., US, Switzerland
15	Megace; megestrol acetate	US6592903 US7101576 US9040088; 208	21.09.2020 22.04.2024 22.04.2024	Sex hormones and modulators of the genital system.	2005	Elan pharma, Ireland
16	Rapamune; rapamycin (sirolimus)	US5989591	11.03.2018	Immunosuppressant.	2002	PF PRISM CV, US
17	Tricor; fenofibrate	US6277405 US6375986 US6652881 US7037529 US7041319 US7276249; 97	09.01.2018 21.09.2020 09.01.2018 09.01.2018 09.01.2018 21.02.2023	Lipid modifying agents.	2004	Abbvie, US
Polymer-based nanoformulations						
18	Copaxone*; glatiramer acetate	US8232250 US8399413 US8969302; 30	19.08.2030 19.08.2030 19.08.2030	Immunostimulants.	1996/2014	Teva pharms, US
19	Eligard; leuprolide acetate	US6565874 US6626870 US8258132; 68	28.10.2018 27.03.2020 28.10.2018	Gonadotropin releasing hormone analogues.	2002	Tolmar therap, US
20	Renagel; sevelamer hydrochloride	US6733780; 44	18.10.2020	Drugs for treatment of hyperkalemia and hyperphosphatemia.	2000	Genzyme, US

1	2	3	4	5	6	7
Protein–drug conjugates						
21	Abraxane; paclitaxel	US7758891 US7820788 US7923536; 66	21.02.2026 03.03.2024 09.11.2023	Antineoplastic agents. Taxanes.	2005	Abraxis bioscience, US
Surfactant-based nanoformulations						
22	Diprivan*; propofol	US8476010 US5908869; 5	01.06.2025 22.09.2015	General anesthetics.	1989	Fresenius kabi, Canada
23	Estrasorb; estradiol hemihydrate	US5629021; 15	31.01.2015	Sex hormones and modulators of the genital system.	2003	Medicis, US
Metal-based nanoformulations						
24	Feraheme, ferumoxytol	US6599498 US7553479; 18	08.03.2020 11.03.2023	Antianemic preparations.	2009	Amag pharms inc, US

*The drug is registered in Ukraine

Table 2. Clinical trials of registered foreign nanodrugs

№	Trademark, active pharmaceutical ingredient	Results	Article
1	2	3	4
		Liposomes	
1	AmBisome; amphotericin B	The safety profile of Amphotericin B Lipid Complex (ABLC) is improved compared with conventional amphotericin B (AmB); ABLC is less nephrotoxic than conventional AmB and can be given safely to patients with pre-existing renal impairment.	Martino R. (8)
2	DaunoXome; daunorubicin citrate	Liposomal doxorubicin and pegylated liposomal doxorubicin demonstrated favorable toxicity profiles with better cardiac safety and less myelosuppression, alopecia, nausea and vomiting compared with the conventional anthracyclines. The better therapeutic index of liposomal anthracyclines without compromising the efficacy makes it a favorable choice over conventional anthracyclines in elderly patients, patients with risk factors for cardiac disease.	Shamudheen M. et al. (9)
1	2	3	4
3	DepoCyt; cytarabine	Encapsulation of cytarabine into liposomes for sustained release prolongs tumor exposure to cytotoxic concentrations of cytarabine, which may improve therapeutic efficacy in patients with neoplastic meningitis secondary to lymphoma or solid tumors.	Murry DJ. et al. (10)
4	DepoDur; morphine sulfate	A new treatment option, a single epidural injection of morphine for continuous perioperative analgesia (DepoDur), may reduce some of analgesic gaps (often related to technical difficulties with the pump or use of an indwelling catheter), the occurrence of hypotension, and compatibility with anticoagulation therapy.	Viscusi ER. (11)
5	Doxil; doxorubicin hydrochloride	Clinical trials have demonstrated that pegylated liposomal doxorubicin (PLD) is equally active but associated with a significantly lower risk of cardiotoxicity compared with conventional doxorubicin whether administered as monotherapy or in combination with trastuzumab. Thus, PLD can be effectively and safely substituted for conventional doxorubicin, allowing retreatment with an anthracycline in the metastatic setting.	Verma S. et al. (12)
6	Inflexal V; influenza virus antigens	Inflexal V has shown an excellent tolerability profile due to its biocompatibility and purity. The vaccine contains no thiomersal or formaldehyde and its purity is reflected in the low ovalbumin content. By mimicking natural infection, the vaccine is highly efficacious. Inflexal V is the only adjuvanted influenza vaccine licensed for all age groups and shows a good immunogenicity in both healthy and immunocompromised elderly, adults and children.	Herzog C. et al (13)
7	Marqibo; vincristine sulfate	Vincristine sulfate liposome injection (VSLI) at its approved dose resulted in a low incidence of clinically meaningful hematologic toxicity. A near doubling of the median dose density did not have an identifiable effect on the reported incidence and severity of hematologic adverse events. VSLI could be well suited for use combined with myelosuppresive drugs and for patients unable to tolerate peripheral blood cytopenia.	Deitcher OR. et al. (14)
8	Mepact; mifamurtide	Mifamurtide (liposomal muramyl tripeptide phosphatidyl ethanolamine; Mepact) is generally well tolerated; adverse events attributed to administration of the drug include chills, fever, headache, nausea, and myalgias. Based on the available data, mifamurtide can be considered for inclusion in treatment protocols for localized osteosarcoma.	Frampton JE. (15)
9	Visudyne;	Photodynamic therapy with Visudyne (liposomal verteporfin), the	Keam SJ.

	verteporfin	first photosensitiser approved for the treatment of subfoveal choroidal neovascularisation (CNV), is a well tolerated treatment that stabilises or slows visual acuity loss in adult patients with predominantly classic or occult with no classic subfoveal CNV secondary to age-related macular degeneration, and subfoveal CNV secondary to pathological myopia or presumed ocular histoplasmosis syndrome.	et al. (16)
Lipid-based (non-liposomal) formulations			
10	Abelcet; amphotericin B	Abelcet has better and improved safety profiles. The pharmacokinetics of Abelcet suggest that lower concentrations in blood due to higher clearance and greater distribution may be responsible for its improved toxicity profile compared to those of conventional formulations.	Adedoyin A. et al. (17)
1	2	3	4
PEGylated proteins, polypeptides, aptamer			
11	Oncaspar; PEGylated L-asparaginase	It is evident that L-asp has a long-term curative effect. However, L-asp is associated with high incidence of adverse reactions. This has prompted the development of pegylated asparaginase (PEG-asp), which has undergone extensive testing. Apparently, PEG-asp has a prolonged half-life with a better tolerance profile while retaining the antileukemic effect.	Liu L. et al. (18)
12	Somavert; pegvisomant PEGylated human growth hormone receptor antagonist	Pegvisomant is generally well tolerated with a safety profile similar to that reported in clinical trials and can effectively reduce IGF-I in patients with acromegaly refractory to conventional therapy.	Schreiber I. et al. (19)
13	Macugen**;** PEGylated anti-VEGF aptamer pegaptanib sodium	Patients with diabetic macular edema (DME) derive clinical benefit from treatment with the selective vascular endothelial growth factor antagonist pegaptanib 0.3 mg. These findings indicate that intravitreal pegaptanib is effective in the treatment of DME and, taken together with prior study data, support a positive safety profile in this population.	Sultan MB. et al. (20)
Nanocrystals			
14	Emend; aprepitant as nanocrystal	Aprepitant adds additional antiemetic protection to standard therapy and should be considered in all patients receiving highly emetogenic chemotherapy.	Olver I. et al. (21)
15	Megace; megestrol acetate	Bioavailability and absorption are greater for nanocrystal dispersion, Megace ES (MA-ES) than Megestrol acetate oral suspension in fasting subjects. MA-ES may be a preferred formulation of megestrol acetate when managing cachectic patients whose caloric intake is reduced.	Deschamps B. et al. (22)
16	Rapamune; rapamycin (sirolimus)	With the application of nanotechnology, NanoCrystal formulation overcomes the problems of formulation, poor bioavailability, and erratic absorption of sirolimus. The tablet formulation has a better palatability, and is more convenient for long-term use. In addition, cost-effectiveness and cost-utility analysis also demonstrated the benefits of long-term use of sirolimus in kidney transplantation.	Shen LJ. et al. (23)
17	Tricor; fenofibrate	Eleven percent of the patients in the study had improvements in their lipid profiles that resulted in achievement of National Cholesterol Education Program lipid panel targets after treatment with the 145-mg nanoparticle formulation of fenofibrate. This improvement in lipid levels may have been related to increased bioavailability of the 145-mg formulation.	Maciejewski S. et al. (24)

Polymer-based nanoformulations			
18	Copaxone; glatiramer acetate	Glatiramer acetate (Copaxone) has been shown in controlled clinical trials to significantly reduce relapse rate and progression of disability in multiple sclerosis with long-term efficacy, remarkable safety, and tolerability. Efficacy as measured by magnetic resonance imaging parallels its clinical benefits as manifested by a reduction in gadolinium-enhancing lesions and brain atrophy.	Dhib-Jalbut S. (25)
19	Eligard; leuprolide acetate	1- and 3-month leuprorelin acetate depot formulations (Eligard/Depo-Eligard) are well tolerated and reliably lower serum prostate-specific antigen and testosterone levels in routine clinical practice.	Braeckman J. et al. (26)
1	2	3	4
20	Renagel; sevelamer hydrochloride	Sevelamer offers a dual therapeutic benefit in dialysis patients – a population at high risk for cardiovascular disease – by improving phosphorus control and the lipid profile, without altering serum calcium.	Burke SK. et al. (27)
Protein–drug conjugates			
21	Abraxane; Paclitaxel	Albumin-bound paclitaxel has demonstrated an advantage over solvent-based paclitaxel by being able to deliver a higher dose of paclitaxel to tumors and decrease the incidence of serious toxicities, including severe allergic reactions.	Kundranda MN. et al. (28)
Surfactant-based nanoformulations			
22	Diprivan; Propofol	Three different propofol 1% formulations-Diprivan (Astra-Zeneca, Cheshire, United Kingdom), Propoven (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro (B-Braun, Melshungen AG, Germany) were compared with either placebo (saline solution) or lidocaine 1% mixed to the propofol solution. Propoven required a higher dose for induction (2.2 ± 0.1 mg/kg) than Diprivan (1.8 ± 0.1 mg/kg) or Lipuro (1.7 ± 0.1 mg/kg; P = 0.02).	Le Guen M. et al. (29)
23	Estrasorb; estradiol hemihydrate	Once-daily application of 3.45 g of micellar nanoparticle estradiol emulsion containing 8.6 mg of estradiol was safe and effective in providing significant relief of vasomotor symptom frequency and severity in postmenopausal women.	Simon JA. (30)
Metal-based nanoformulations			
24	Feraheme, ferumoxytol	In patients on hemodialysis, rapid intravenous injection of 510 mg of ferumoxytol led to significantly greater hemoglobin increases compared with oral iron, with comparable tolerability.	Provenzano R. et al. (31)

According to the analysis the leading countries of the world to create a favorable climate for innovation have used the practice of public and private partnership and project financing in the implementation of large-scale and socially significant projects, thereby reducing the risk to the individual investor.

The complexity of the legal protection of intellectual property leads to the use of the following recommendations: identifying the maximum number of direct effects and additional technical features of nano-objects due to the diversity of their properties; combined "nano features" with features of traditional technology to produce new positive qualities due to their interaction; concealment of know-how by bringing extended range operation of processes. In some cases, especially when there are doubts about the grant of a patent, it is advisable to postpone substantive prosecution. Because scientists can be opened new properties of nano-objects: nanoemulsions, fullerenes, nanotubes, etc. and this will increase the likelihood of acquisition of patent.

CONCLUSION

It has established features of the patent researches of nanotechnology-based drug development. It has offered the algorithm of the patent researches, which takes into account the search in patent databases and

scientific resources, the use of the International Patent Classification, the European Classification, the United States Patent Classification and specific keywords, top pharmaceutical company names in the nanotechnology field.

It has found out active patenting of nanoparticles as the pharmacologically active substances and their technologies, nanoparticles for drug delivery. It has established that nanotechnology has used for the drug developments of most pharmaceutical groups.

The studies indicate the prospects and feasibility of nanotechnology-based drug developments in the form of nanoparticles, as well as the nanocontainers with high pharmacological activity, bioavailability and safety. The high costs of the creation of such drugs are justified in medical practice, especially in the treatment of tuberculosis, AIDS, cancer, and others. There is no doubt that the success of the creation, production and use such drugs is the presence of an effective system of patent protection.

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