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Review Article

COMPLEX GENERICS AS A TREND OF MODERN PHARMACEUTICAL DEVELOPMENT

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ABSTRACT

In the perspective of the pharmaceutical industry development, manufacturers expand their product portfolios by updating generic drugs. Complex Generics (CG) or Nonbiological Generic Drugs (NBGD) contain known pharmaceutical substances are out of patent protection and are made by using new technologies, excipients, nanocarriers, dosage form modernization, etc. These drugs are developed in the patients' interests to improve their life quality and increase drugs' efficacy and safety.

The article discusses the categories and characteristics of CG, shows examples available on the pharmaceutical market, API and dosage forms. This article discusses approaches to quality control that pose challenges for developers and regulators. The fundamental importance of the innovative drugs manufacturing process and the ingredients standardization in the dosage forms formulations to create the standard product are indicated. First, a comprehensive control of polymers is required as an important tool to make the necessary pharmacokinetics. The influence degree on the API release and the effectiveness of dosage form (DF) depends on the polymer's physicochemical characteristics. In this regard, it is important to create databases of these excipients accessible to developers containing information about properties, use, dosages and safety.

In view of the complexity structure and manufacturing processes of the NBGD and insufficiency of pharmacopeial requirements for standard approaches for resolving issues of comparability and bioequivalence the current regulatory documents should be expanded and revise for a correct quality assessment. There is a need to create new scientific and regulatory roadmaps for the development and approval of complex generic drugs.

Keywords: Complex generics, Non-biological generic drugs, Innovative dosage forms, Nanodrugs, Pharmaceutical development, Dosage forms, Standardization

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INTRODUCTION

Recently, experts identified two ways to create drugs: the first was to develop original drugs containing the original patented molecule of the active pharmaceutical ingredient (API), the second was to obtain reproduced drugs, which are copies of the original ones.

Often the development of original and generic drugs is carried out by pharmaceutical companies in parallel. Promotion strategies are significantly different for these drugs–original drugs are heavily advertised and promoted by doctors, retailers or pharmacists and are branded drugs. Generics are usually not promoted despite the fact that both drugs contain the same API. Consequently, the formulations of both drugs are similar, but the price of the branded drug is higher [1].

Because of the manufacturing of generics, the healthcare need for affordable medicines was satisfied. Currently, the share of generic drugs in the markets of developed countries reaches more than 89%. Considering that the generics prices are 75% (or more) lower than the originators prices, there is the obvious economic feasibility for patients and the healthcare system, including insurance companies, of the presence of generic drugs on the market [2]. Thus, the need for both expensive original drugs and generic drugs affordable to the general population become obvious.

The development of technologies affects to approaches of drugs creation. In recent decades, there is a strong trend of both foreign and domestic developments towards the creating generic drugs improved forms containing long-known and well-established APIs that have come out of patent protection. Generics modernization is carried out in the patients' interests to improve the quality of their life, increase the effectiveness and compliance of therapy. The updated generics, called "supergenerics" in some scientific publications, have new level of efficacy and reduced side effects, as well as expand the traditional use of known drugs. The introduction of generics to the market is faster than original drugs and gives good results, so it will develop [3, 4]. According to data [4], the volume of the generic drugs global market that are not copies of the original ones was estimated at 387.92 billion US dollars in 2020 and is projected to reach 675.29 billion US dollars by 2030, so the average annual growth rate in the forecast period will be 5.7%. The modern forms of generic drugs production are actualized by the fact that many top original APIs are out of patent protection at present [5]. According to forecasts [6, 7] in the next decade, there will be the four best-selling drugs in 2020: Humira (AbbVie), Keytruda (Merk and Co), Revlimid (Bristol Myers Squibb) and Eliquis (Bristol Myers Squibb/Pfizer).

This article presents a brief overview of complex generics as an innovative area of modern pharmaceutical development, approaches to their creation and quality control. The data for the review were based on the following sources: PubMed, Scopus, as well as open internet sources, including FDA, EMA, and WHO websites. The search was performed during the years 2022-2023 using the following keywords: complex generics; non-biological generic drugs; innovative dosage forms; pharmaceutical development, drug development.

Terms

As already mentioned, a new generation of generic drugs are called "super-generics" contain known out-of-patent substances, but do not fit the term "generic drugs". These drugs are not simple copies, since differ from the originals in the structure of the dosage form, or in the modification of the active substance by specific carriers, or in another way of administration, or in a combination of already known active ingredients, or in another sign [8]. In the regulatory documents of the Russian Federation, EU, USA, there are no definitions for the term "super-generics", such as there is no classification. However, many issues and problems associated with the development, quality assessment, production and registration make it necessary to analyze and summarize various aspects of the

direction for creating and bringing to the market improved types of generics, or "supergenerics".

The FDA [9] formed a list of drug groups calling "Nonbiological Generic Drugs" (NBGD) (table 1).

Table 1: Categories and characteristics of NBGD according to the FDA [9]

Categories	Examples	Reference
CG with complex active ingredients	Peptides, polymeric compounds, complex mixtures of active ingredients, ingredients of natural origin	[9]
CG with a complex composition	Liposomes and colloids	[9]
CG for complex or new delivery route	Local drugs: dermatological and complex ophthalmic, as well as ear (auricular) dosage forms in the forms of suspensions, emulsions or gels	[9]
Complex dosage forms	Transdermal, metered-dose inhalers and, extended-release injectables, etc.	[9]
Complex drug-device combinations	Autoinjectors, metered-dose inhalers	[9]
Other	Other drugs, which complexity or uncertainty of the standardization, ways of approval need new scientific research	[9]

NBGD-Nonbiological Generic Drugs

As it shown in the presented table, NBGD can be composed of synthetic or semi-synthetic APIs of complex chemical structure. NBGD are also called "non-biological drugs" due to the origin of active substances [2]. The main difference from biological drugs is that the molecules of the active ingredients of generic drugs are usually smaller, simpler and easier to copy. Biological products, on the other hand, contain active components having complex structure and are obtained from living sources, such as bacteria, yeast and animal cells. It cannot be copied exactly because it usually contains a mixture of many minor variations of compounds, and this mixture is not the same in every dose or batch of product [10].

NBGD include drugs based on carriers of various structures: liposomes, nanoparticles, micelles, etc. Due to the more complex design of dosage forms, the determination of pharmacopeial quality indicators (physicochemical, quantitative, biopharmaceutical, etc.) is complicated and is insufficient to prove pharmaceutical equivalence and bioequivalence in comparison to the original drug. The carrier type and material, the interaction with the API and the parameters of its release from the carrier determine the therapeutic effect of such drugs [2].

In recent years, co-crystals have also become an interesting area of research and some regulatory agencies have created regulatory standards for them, which has resulted in the approval of these crystals for sale. New guidelines from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have made the manufacture and standardization of co-crystals less complicated [11].

There has been a significant increase in the use of microsphere systems, which can be used in a number of drug products due to the types of polymers suitable for the intended release target. Microspheres have numerous advantages: they have minimal adverse effects, longer therapeutic effects, require fewer doses and provide more uniform drug absorption. In addition, they are adaptable, provide effective encapsulation and are cost-effective [12].

No less complex are the API-device combination CGs. Dry powder inhalers and extended release injectables can be examples of this category of NBGD products, which require scientific development of specific tests for quality assessment [2, 9].

The common features of the NBGD listed in the table are containing APIs out of patent protection with a simple and more complex structure; therefore it is not the original drugs and not their simple copies. If the parameters and test methods, as well as the ways to bring originators and generics to the market now are defined and understood, it is not applicable to NBGD due to the complexity of design, composition, and a new method of application needs development and research.

In the EU and the EAEU complex generics can be classified as hybrid drugs that are neither original nor reproduced. However, approaches to understanding this term are slightly different, which follows from [13]. According to the EMA, hybrid drugs include generic drugs are similar to the original ones but differ in effectiveness (different strength), method of administration or indications for use, shown by the clinical trials. Standard test procedures are used to standardize hybrid drugs [14].

Drugs that can be classified as complex generics

The first supergenerics began to be used at the turn of the millennium.

The FDA approved the taxol super generic Abraxane® for the treatment of metastatic breast cancer in 2005. The active substance is nanoparticles of paclitaxel bound to albumin, which replace Cremophor, so there is a reduction of side effects, such as joint and muscle pain, and an increasing the tumor response to therapy. Coating taxol with albumin allowed using it without steroids, which can cause problems range from insomnia to hyperglycemia, etc. [15]. The drug is produced in the form of a lyophilizate for the preparation of a suspension for infusion.

Sandostatin® LAR [16] by Novartis Pharma Stein, AG (Switzerland), containing octreotide acetate (a synthetic analogue of somatostatin) as an active substance and intended for intensive therapy in gastroenterology, is produced in the form of microspheres from a branched copolymer of lactic and glycolic acids for the preparation of a suspension for intramuscular administration. The solvent is a solution of carmellose sodium and mannitol in water for injection. The drug was registered in the USA in 1997 [17].

An example of NBGD is a combination drug device Trelstar® [18] manufactured by Debiopharm Research and Manufacturing SACH-1920 Martigny, Switzerland for hormonal therapy in the palliative treatment for prostate cancer. The active substance is triptorelin pamoate (gonadotropin-releasing hormone agonist) in the lyophilizate form containing microgranules obtained using a star-shaped branched copolymer of poly-D, L-lactic and polyglycolic acids. In addition to microgranules with API, the drug composition includes mannitol, polysorbate 80, sodium carboxymethylcellulose. The Telstar® packaging, in addition to the vial with lyophilized microgranules, includes a syringe pre-filled with water for injection and the original MIXJECT SYSTEM device (fig. 1) manufactured by West Pharma Services IL, Ltd, Ra'anana, Israel. MIXJECT SYSTEM is designed for dispersing the lyophilizate in a solvent with subsequent collection of the drug into a syringe. These procedures are complicated by the presence of a polymeric microspheres' suspension in the lyophilizate. Using MIXJECT a vial with a lyophilizate is opened, water for injection is supplied into from an attached syringe, then the suspension dispersed in water is drawn back into the syringe with a plunger, the vial is disconnected, and a needle is installed on the syringe [18].

The drug is available in three dosages, depending on which the duration of action after a single injection ranges from 4 to 12 w.

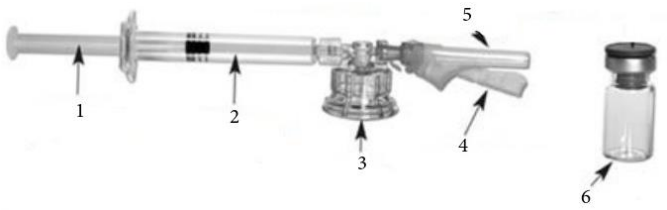

Fig. 1: A system for lyophilizate feeding to a syringe for Telstar® drug [13], 1-plunger rod, 2-syringe barrel, 3-vial adapter, 4-needle shield, 5-safety cover, 6-vial

Among the first versions of super generics are widely used till now Diprivan® (propofol, an anesthetic, 1991 FRESENIUS KABI), Copaxone® (glatiramer acetate injection, for the treatment of multiple sclerosis, 1996, Teva), Doxil® (doxorubicin hydrochloride liposomal, anticancer drug, 1996 Sequus Pharmaceuticals), Lovenox® (sodium enoxaparin for injection, antiplatelet agent, 1993 SANOFI AVENTIS), Ferrlecit® (stable iron and sodium gluconate complex in sucrose, anemia, 1997, RHONE-POULENC RORER) [19-24]. As it shown from the above examples, NBGD manufacturers use different approaches to improve the quality of drugs: coating API with albumin, microspherization, using an original and complex system for feeding the dosage form into a syringe, etc.

Despite the fact that many NBGD are known for several decades, these have considered as an alternative to generic and original drugs literally in recent years. The prospects for the NBGD creation are justified by the use of modern ingredients and the rethinking of some factors influencing their effectiveness, for example, the route of administration, the type of dosage form, etc.

The most important factor in the emergence of NBGD was the use of technologies discovered after the 70s of the 20th century and today already well-studied, so these drugs can be considered not scientific but innovative.

Since 2018, over 100 complex generic drugs have been approved annually in the USA [25]. The information analysis of the complex generic drugs registration allows understanding the current situation more detailed using the FDA data as an example [9]. At the end of 2020, FDA revised and approved the specifications for 31 drugs, and 45 more were under consideration. In the first echelon (revised), most of the DFs are traditional, soft DFs for external use are leading. Only 3 drugs are complex and amount to 9.7%; these are the intrauterine device with levonorgestrel, capsules with improved release of oxycodone and pellets for implantation with testosterone.

In the second echelon complex, DF was already 20%. Among them are: controlled release subcutaneous implant with afamelanotide, colesevelam hydrochloride chewing pad, extended-release periodontal system containing doxycycline hyclate, vaginal ring with ethinyl estradiol and segesterone acetate, exenatide increased release subcutaneous suspension, irinotecan hydrochloride liposomal injection, intrauterine device with levonorgestrel, mometasone furoate implant, vaginal system with progesterone. The range of complex dosage forms indicates that scientific developments are more actively mastered by manufacturers and, thus, become on a par with traditional dosage forms.

Among the active substances of CD, low molecular weight (acyclovir, levodopa, meloxicam, lidocaine, midazolam, etc.), antibiotics (tobramycin, penicillin benzoate, clindamycin, doxycycline, etc.) are used, and substances of complex structure: synthetic and semi-synthetic hormones, peptides, etc.

Features of development and quality control

Approaches to testing and the regulatory framework for quality indicators of NBGD in innovative dosage forms cause many questions and difficulties among developers and regulators, hindering their introduction to the market. Due to the original design, NBGD need special additional standardization methods. These methods based on not only the active substances analysis and the pharmacopeial indicators determination. Knowledge of the technological obtaining features and the structure of dosage forms, taking into account new aspects of testing excipients, is also important. Differences in the nature and structure complexity of APIs, new application methods, technologies for creating dosage forms and quality indicators cause new challenges. These challenges are not only in the development of standardization, but also in the manufacturing process control *in vivo* research to assess the efficacy and safety of NBGD and resolve the issue of clinical comparability. Now these tasks require solutions.

The production of generic drugs represents a savings to patients and hospitals, and these drugs should be evaluated periodically. To determine whether the drug is safely substituted, *in vitro* efficacy evaluation is very important [26].

In 2020 the FDA awarded a grant to the University of Maryland, Baltimore and the University of Michigan to establish The Center for Research on Complex Generics (CRCG) to solve the problems associated with the development of NBGD. The tasks of the Center include promoting cooperation between interested scientific organizations and other developers of drugs, conducting joint research, exchanging experience and information between the FDA, the scientific community and companies producing NBGD, training researchers involved in development. The activities of the Center will make new approaches to the NBGD development, quality assessment and bioequivalence determination more accessible and understandable [27].

In December 2020 the Center conducted a survey of researchers working in the field of development and study of complex generic drugs to determine the urgent tasks in the development of non-biological DF should be focused on first. The survey covered three areas: identifying the most relevant types of complex products, identifying research methods to confirm the bioequivalence of these products and identifying priority educational topics for CRCG [27].

The top three most problematic NBGD cause difficulties for researchers in the development and quality assessment include complex injectable drugs, complex formulations and nanodrugs; combined medicines; inhalation and nasal forms.

Test methods modeling local pharmacokinetics on a physiological basis, oral absorption and bioequivalence models and data analysis and machine learning cause difficulties the most.

As for educational topics, the most popular were related to complex injectable drugs, including prolonged ones, long-acting implants, drugs with complex compositions and nanomaterials, combined medicines. The analysis of experimental data, including quantitative methods and modeling, raises many questions. The results of the survey formed the basis of the Center's initial research and educational programs.

To help developers the FDA created a web-page with information about reviewing product-specific guidelines for complex generic drugs submitted for approval. There are recommendations based on new scientific information that ultimately help pharmaceutical companies plan and optimize the development of NBGD [9].

The manufacturing process of innovative CGs is a base for creating the right standard product. It follows the path of scaling innovations, which justifies the development of new technological solutions, the need for special attention and precise compliance with certain technological conditions. Even small changes for simplification and reduction in cost can affect the quality of the drug. The

manufacturing process must be stable include constant monitoring of technological and other conditions, validation, as well as the use of identical standard excipients.

Innovations are leading to the creation of a new segment of supergenerics with improved therapeutic effects. These drugs are cost-effective and also provide greater patient compliance, which directly contributes to meeting the medical needs of the masses. This new segment gives a modern outlook to the generics market, following the quality by design (QbD) approach to develop improved therapeutics [28].

QbD is used in pharmaceutical processes to create a pre-determined product quality. QbD is a science-based approach to reduce process variability and create process control strategies that result in improved process understanding and reliability. A requirement of QbD is the identification of all critical recipe attributes and their associated process parameters. Thus, the QbD approach is a tool for developing efficient and quality pharmaceutical products [29].

If the production chains for obtaining various NBGD in most cases are individual and refer to know-how, then the properties of excipients are reflected in open sources. The choice of an inactive component or its replacement is not an easy case to decide because of the large and constantly expanding range diverse functional characteristics of modern pharmaceutical-grade excipients.

Therefore, databases of pharmaceutical ingredients become relevant in purpose to systematize and provide complete and comprehensive information to help drug developers. Guidance on inactive ingredients used in drug formulations was first issued in the U. S. in 1987 in paper format; posting to the FDA's online database began in 2003. The FDA database contains information about dosage forms in which excipients are used, the maximum daily dose, acceptable routes of administration, dosages for each of the indicated routes of administration (for which data are available), as well as safety information [30].

Available information on inactive ingredients is constantly being updated so that users can perform electronic queries to obtain accurate information about ingredients.

The control of ingredients as an important tool for the necessary pharmacokinetics of DF becomes relevant. First of all, this applies to polymers, the degree of their influence on the release of API and the effectiveness of DF depends on the molecular weight, branching of the polymer chain, the ratio of components in copolymers and other characteristics. Therefore, in addition to identification the content of the polymer and impurities, it is extremely necessary to determine and quantitatively declare a number of its physicochemical properties [9, 31].

Many long-acting drugs based on polymers, such as biodegradable microspheres, in situ gels and implants are intended for parenteral and ophthalmic routes of administration. The physiology of these routes of administration takes special requirements for the quality of drugs. Among the polymers used in formulations to control the rate of API release and prolongation of its action are D, L-polylactic acid and its copolymers, approved for pharmaceutical use since the 90s of the 20th century.

Non-proprietary analogues containing a copolymer of polylactic and polyglycolic acid (PLGA) cause problems in the characterization and evaluation of quality indicators. To address issues related to generic PLGA development, the FDA established an extensive research program to explore new methods and tools to aid both product development and regulatory review. The main objects of research are analytical tools for the characterization of PLGA polymers; the impact of PLGA characteristics and manufacturing conditions on product characteristics; *in vitro* drug release testing, correlation of *in vitro* and *in vivo* results, modeling techniques to facilitate formulation development and design of bioequivalence studies of PLGA-based drugs [32].

In recent years, to create new drugs scientists use not only linear but also star-shaped and branched polylactides and their copolymers [31, 33]. Since the properties of branched polymers are highly dependent on the architecture of the constituent macromolecules, a detailed knowledge of its topology is an important component for determining the structure-property relationships of the resulting product. In order to ensure the standardization of drugs, the release profile of API from, which is determined by the polymer, information on the type of polymer, the degree of its branching, and concentration is needed.

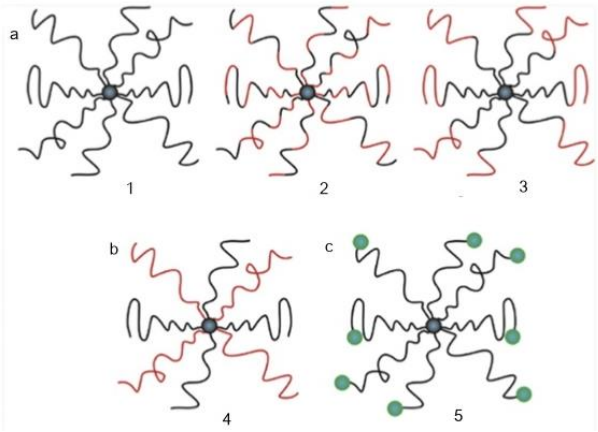

Fig. 3: Illustration of variuos star polymers classified by (a) compositon and sequence distribution of the arm polymer, (b) difference in arm species, and (c) functional placement [25]. 1-homopolymer, 2-random copolymer star, 3-block copolymer star, 4-compositional miktoarm star, 5-end-functionalized homopolymer star

Determination of the star-shaped polymers characteristics consisting of nonlinear architecture macromolecules is complicated in comparison with their linear counterparts. Work in this direction has begun, it has become possible to characterize complex branched star-shaped polymers in the formulations of Sandostatin® LAR, Trelstar®, and others [31] with the development of advanced analytical methods. For this, precise instrumental analytical methods are already used today: proton nuclear magnetic resonance, desorption-ionization time-of-flight mass spectrometry, differential scanning calorimetry, thermogravimetry, wide-angle X-ray diffractometry, and more and more research use structure visualization methods: atomic force microscopy and transmission electron microscopy [33].

The list of critical quality indicators of block copolymers and micellar drugs based on is given in [34]. The key quality indicators of block copolymers, as other excipients in drug formulations, are chemical structure, nature of the bond with API, impurities.

However, the list of polymer micellar drugs characteristics recommended for study is not limited to this. These features are also included:

-related to the polymer micelle: average micelle size and micelle size distribution profile, zeta potential, morphology, stability, release of the active substance in plasma and/or significant medium, degradation of the block copolymer in plasma and/or significant *in vitro* medium;

-related to the manufacturing process of micelles, primarily the stability of the manufacturing process and ensuring the constancy of DF indicators, validation of recovery processes and ensuring sterility, etc.;

-related to the behavior of micelles *in vivo*, affecting the rate and site of the API release, as well as the rate and site of the block copolymer degradation.

Strict requirements for the quality of excipients determine the production in accordance with good manufacturing practice (GMP). According to the FDA, the NBGD master file should contain a section related to the production of inactive ingredients, including basic technical details.

As mentioned earlier, in order to confirm the quality of NBGD based on nanoparticles, liposomes, polymers, etc. carriers, as well as complex preparations equipped with special devices for administration, it is necessary to develop scientifically specific quality indicators and determination methods and standards not described in pharmacopoeias. For example, the API release test *in vitro* from long-acting drugs causes difficulties for developers [35]. The monographs USP, EP, RF describe the apparatus and conditions for carrying out standard procedures for the Dissolution test, however, testing of NBGD for example, for injectable suspensions, needs to be optimized for a specific route of administration and duration of release of API from DF. In [35], it is recommended to evaluate the release *in vitro* in real time during the expected period of use of the product. Accelerated testing can also be used as a quality control tool, in which the temperature or medium or flow rate of the flow cell is changed to stimulate drug release. However, accelerated testing should be supported by cross-validation with long-term testing to demonstrate the interchangeability of the proposed tests as a quality control tool.

The scientific complexity of many CG makes it difficult to establish pharmaceutical equivalence and/or bioequivalence.

Because of the new design of the dosage form, the introduction of new excipients and other changes, the behavior of NBGD in the body may differ significantly from the behavior of the active substance of the known drug. In the case of delivery systems such as micelles, nanoparticles or liposomes, the entire carrier-PI complex is the active pharmaceutical ingredient and its properties cannot be fully characterized by physicochemical analysis alone [36]. Therefore, the study of the pharmacokinetics and bioequivalence of CG is necessary. For the correct and safe use of CG, it is also necessary to study pharmacodynamics, determine the pathways of metabolism and excretion not only the active but also a number of excipients, in particular, of a polymeric nature [34, 36, 37].

The Board of the Eurasian Economic Commission has developed a number of Recommendations designed to ensure the use of unified approaches to pharmaceutical development, quality assessment and pharmacokinetic and clinical studies of bioequivalence of certain groups of drugs:

-block copolymer micellar drugs [37];

-drugs for parenteral administration coated with nanoparticles and drugs based on colloidal iron for intravenous administration [37];

-liposomal drugs for intravenous administration [34].

The EEC guidelines cover a whole range of issues from general quality requirements for the indicated groups of drugs and their ingredients to the strategy of pharmaceutical development, preclinical and clinical studies and clinical safety assessment. These guidelines contain the currently available scientific potential of the CG developments of these groups, which is the result of research by scientists for decades and is reflected in scientific publications. The most difficult question is the choice and justification of specific methods and standards, because there are not in the existing regulatory documents related to the creation of CG. Due to the complexity of structure and manufacturing processes, the current regulatory documents need to be expanded and revised.

Given the potential and prospects of NBGD, it is important not only to ensure clarity in the procedures for evaluation and publication of scientific studies. There is a need to create new guidance documents scientific and regulatory roadmaps for the development and approval of generic versions of complex drugs [38].

The development of complex generic drugs aimed at unmet clinical needs is a non-trivial task; it [25, 27, 31, 35, 36] has become a growing segment of the pharmaceutical industry, setting the development vector for pharmaceutical sciences, technologies, production, dictating new approaches to drug quality control. The interest in the creation of CG among a number of pharmaceutical manufacturers leads to the reconstruction of their business models. Among the key companies working in this direction are: Sun Pharmaceutical Industries Ltd., Meda Pharmaceuticals Inc., Taiwan Liposome Company Ltd., Dr. Reddy's Laboratories, Allergan plc., Teva Pharmaceutical Industries Ltd. and Celgene *et al.* [39].

Lubrizol Life Science's Health (LLS Health) has many years of experience in working with a number of dosage forms, including injections of microcarriers and depot gels, implantable systems and combined drugs, as well as various sterile ophthalmic dosage forms [31, 35].

A detailed report on the CG market development in the world is given in [39]. It provides an overview of the CG approved in 2016-2018, includes information on the administration routes, pharmacological action. Solutions for the development of CG are presented; important technical characteristics associated with technologies, the type of substance molecule, the influence of various factors on the properties of the drug are shown. Because of a detailed analysis of the trends, it was concluded that the CG market is ready for significant growth in the coming years. The Asia-Pacific region is expected to see the best opportunities for its growth due to the presence of key manufacturers that focus on innovation.

CONCLUSION

In the perspective of the pharmaceutical industry development, manufacturers expand their product portfolios by updating generic drugs. Complex generics based on innovative technologies, new components, updated dosage forms, new routes of administration, etc. are used to improve the quality of patients' treatment by increasing the effectiveness and safety of drugs. The development of CG in most cases cannot be attributed to trivial tasks, since it entails the need to solve complex technological and analytical issues. Manufacturers of CG introduce nanotechnologies, new complex excipients and other innovations into practice that becomes vectors of scientific and commercial development of the pharmaceutical industry. The evolving trend of creating CG as generic updates pose the challenge of improving regulatory procedures and guidance documents, as well as regulatory recommendations on issues related to determining the quality, safety and efficacy of new versions of reproduced drugs. The creation of a legal regulatory framework to substantiate the principles of standardization, the generalization of existing approaches to the creation of CG are relevant today since it will accelerate the entry into the market of effective, standard drugs and serve as an incentive for the development of promising area of pharmaceuticals in the future.

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AUTHORS CONTRIBUTIONS

Demina N. B.–idea and design of the research, writing the text of the article, Bakhrushina E. O.–idea, writing of the article, participation in the discussion of the design, Merkushova A. G.–gathering

information, participation in the discussion of the article, Pomytkina M. V.–writing the text of the article, Anurova M. N.–participation in the discussion of the article, reviewing, Bardakov A. I.–participation in the discussion and writing of the article, Rastopchina O. V.–participation in the discussion and writing of the article, Krasnyuk I. I.–reviewing, final approval of the article.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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