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Review Article

Revision of pharmaceutical legislation in the context of antimicrobial resistance and challenges facing the introduction of innovative antimicrobial medical products in Europe

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Abstract

The presented article provides a systematic review of the pharmaceutical legislation (EU Pharmaceutical Package) – the current proposal of the European Commission for a new Directive, repealing and replacing Directives and modifying Regulations of the European Parliament and of the Council, incorporating the relevant parts of the Regulation concerning medicinal products for pediatrics, Regulation for orphan drugs and others, aiming at revision of the pharmaceutical legislation in the context of antimicrobial resistance and challenges facing the introduction of innovative antimicrobial medicines in Europe. It outlines a critical analysis on the impact of the changes in the context of introduction of innovative antimicrobial medicinal products with an emphasis on unsatisfied medical demands of the European population. The revision of the pharmaceutical legislation provides an argument to consider that the proposed Pharmaceutical Package could resolve some of the issues associated with the access to novel antibiotic medicines. It is necessary to find a consensus and a balance between, on the one hand, meeting the need for antibiotics for the citizens of the European Union and, on the other hand, providing timely access to generic medicines to meet the needs of the population.

Keywords

revision, pharmaceutical, legislation, antimicrobial resistance, innovative, medicinal products

Introduction

The present article provides a systematic review of the revision of the pharmaceutical legislation (EU Pharmaceutical Package) – current proposal of the European Commission for a new Directive, repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC of the European Parliament and of the Council incorporating the relevant parts of the Regulation concerning medicines for pediatric use (Regulation (EC) № 1901/2006), as well as a new Regulation repealing and replacing Regulation (EC) № 726/2004 and Regulation on orphan drugs (Regulation (EC) № 141/2000) and repealing the Regulation on pediatric drugs (Regulation (EC) № 1901/2006) incorporating its relevant parts European Commission (2023). Antimicrobial resistance is a growing public health concern in Europe. The inappropriate and irrational use of antibiotics in hospitals and outpatient settings is one of the driving factors of antimicrobial resistance according to Chin W et al. (2023). Bulgaria has shown a trend towards increased administration of anti-infective medicines in recent years according to Vankova et al. (2023). A literature review, conducted in 2023 by Lebanova et al., outlined irrational use of antibiotics as the most frequent cause of antibiotic resistance. On the other hand, the judicious use of antibiotics can prevent the occurrence and selection of resistant bacteria, even enabling reduction of antibiotics use, thus leading to a low rate of *Clostridiumdifficile* infections as stated by Davey et al. (2017) That is why the next few years will be of great importance for the provision of global awareness and readiness for counteracting antimicrobial resistance (AMR). The results of a predictive statistical model published in Lancet with authors Murray et all (2022) assessed about 3.62 to 6.57 million deaths associated with bacteria resistant to antibiotics in 2019 including 1.27 million deaths that could be directly assigned to it. In this context, the public sector – national governments – has a major role in incentivizing the development and market access of novel antimicrobial medicinal products and in creating prerequisites for better coordination between the regulators – national competent authorities and the European Medicines Agency (EMA). If AMR continues to increase, it will result in approximately 10 million deaths per year globally and to a loss of 2% to 3.5% of the global GDP according to the study conducted by the European Commission.

Just because of that reason in 2021 the European Commission established the Directorate-General for Health Emergency Preparedness and Response Authority (DG HERA) with the mission to prevent, detect and rapidly respond to health emergencies such as the threat of infections, insensitive to the currently marketed anti infectious medicinal products as stated by Murray et al. (2023)

With this mandate, DG HERA is in a good position to manage that issue in cooperation and coordination with other Commission initiatives in the framework of the EC's One Health plan on antimicrobial resistance, European Commission (2022), Delesalle et al. (2022).

Following a comprehensive literature review (intermediate report), complemented by surveys and consultations between 22 EU Member States and more than 90 stakeholders on antimicrobial resistance (AMR), the following three recommendations on the DG HERA`s in this field were outlined, European Commission (2023):

1. Support in the implementation of incentives for the introduction of innovative antibiotics in Europe.
2. Coordination of the efforts of national governments and European interested parties, including contribution in the form of financial incentives.
3. Provision of coordination, sharing of knowledge and provision of non- financial support. This includes distribution of best practice and building capacity in the member states.

National context

Mestrovic et al. (2022) estimates the highest overall mortality rates for *E. coli*, resistant to all antibiotics have been revealed in Bulgaria, with a mortality rate of 7.29 individuals per 100000 population and 29 cases associated with antimicrobial resistance. Bulgaria has also achieved the highest overall mortality rates for resistant *K. pneumoniae*, with 4.59 and 14.70 per 100000 population, respectively. According to a survey published by Mestrovic et al. (2022) the level of antimicrobial resistance in Bulgaria ranks second after Greece. This survey made a comparison between all EU Member States, juxtaposing data from 2015 and 2020. In 2020 Bulgaria, Greece and Romania detected almost 20% increase in reported cases of antibiotics resistant infections Unfortunately, Bulgaria has not yet adopted the National program for rational administration of antibiotics and surveillance of antimicrobial resistance, which was developed back in 2019. On the other hand, positive steps have been reported in relation to the digitalization in the health sector as it enabled the monitoring of the process. The electronic prescription as a component of the National Health Information System (NHIS) was introduced during Phase 2 of the implementation of the system and has been functioning since June 2021 covering the prescribing and dispensing of products with the so called "white" prescriptions, which are fully or partially reimbursed by the National Health Insurance Fund (NHIF), becoming mandatory for this type of prescriptions from that date. Since July 2023 the electronic prescription has been mandatory also for medicinal products with special regime of prescribing and dispensing (so called "yellow" and "green" prescriptions). The digitalization of prescribing and dispensing of antibiotic medicines established prerequisites for reliable surveillance and monitoring of AMP and their use, including following the trends, at all levels in humane medicine. They are of crucial importance for the assessment of AMP and to support the appropriate use of antimicrobial medicinal products. Mandatory electronic prescribing of medicines, classified as "Medicines for the treatment of diabetes" or "Anti-infectious medicines

for systematic use" has been functioning in Bulgaria since 16 October 2023 according to Ordinance No. 4 of 4 March 2009 of the Ministry of Health (2023).

The aim of this survey was to make a review and revision of pharmaceutical legislation in the context of antimicrobial resistance and to present the challenges facing the introduction of innovative antimicrobial products in Europe.

Material and methods

A systematic review was conducted using the PRISMA method analyzing data from various information sources, including articles and official announcements of the European Commission, the European Center for Disease Prevention and Control (ECDC), the World Health Organization and the European Medicines Agency, as well as publications from the scientific databases PubMed, Elsevier, Google Scholar. Various European and national regulations were reviewed during the data analysis.

Of the quoted databases and other institutional information sources the team selected and sorted 88 potentially relevant articles and information sources. After eliminating duplicates, the review included a total of 71 information sources. The comprehensive review of all 71 selected information sources excluded another 47 sources as they did not contain sufficient data and/or because the information was irrelevant at the time of the review. As a result of those actions this paper presents the analysis of the full text of 24 articles (Fig. 1).

Discussion

In July 2022 the European Commission and EU Member States identified AMP as one of the three biggest health hazards of basic priority. On 13 June 2023 the Council adopted a recommendation concerning strengthening EU activities for counteraction of antimicrobial resistance through the approach "One Health". Together with all measures related to infections control and prevention, an emphasis was also placed on strengthening the surveillance and monitoring of AMP and the use of antibacterial medicinal products as stated by the European Commission (2023).

Revision of pharmaceutical legislation in the field of antimicrobial resistance

The acting EU legislation in the field of pharmaceutical products includes both general and specific regulations. Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) № 726/2004 of the European Parliament and of the Council (called together "general legislation in the field of pharmaceutical products") lay down the rules relating to the authorization of medicinal products and the requirements, applicable after the authorization has been issued, pre-authorization supportive designs, regulatory incentives associated with data and marketing protection, manufacturing and supply, as well as rules relating to the European Medicines Agency (EMA). The general legislation in the field of pharmaceutical products is complemented with specific legislation

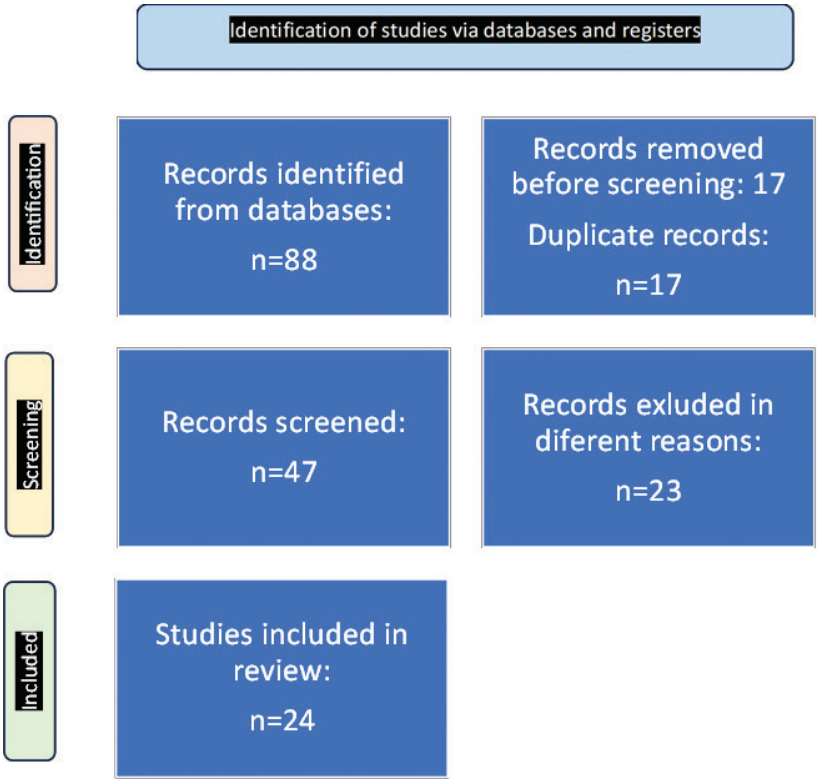

Figure 1. PRISMA flow chart for the selection process of articles.

referring to medicinal products for rare diseases (Regulation (EC) № 141/2000 – "Regulation on orphan medicinal products"), on medicinal products for pediatric use (Regulation (EC) № 1901/2006 – "Regulation on medicinal products for pediatric use") and on advanced therapy medicinal products (ATMP) – Regulation (EC) № 1394/2007 – Regulation on ATMP.

In this regard, on 26 April 2023 the European Commission published a package of regulatory proposals in the field of pharmaceutical legislation at European level (Pharmaceutical package). The package provides a comprehensive revision of the acting EU regulations and incorporates propositions for a new Directive and a new Regulation, revising and replacing the existing pharmaceutical legislation, including the legislation on medicines for pediatric use and orphan drugs. The aims of the Pharmaceutical package are multidirectional: it is a package associated with human life and health, but it also has economic dimensions related to the competitiveness of the European pharmaceutical industry. Access, availability, and affordability are among the most important aspects of the Package. Together with that a modulation is foreseen in the incentives system for innovations and, in particular, encouraging the development of innovative antimicrobial products, guaranteeing their appropriate use, and strengthening the environmental risk assessment as part of the marketing license.

The suggested reconsideration of the pharmaceutical legislation consists of two proposals:

- New Directive, repealing and replacing Directives 2001/83/EC and 2009/35/EC of the European Parliament and of the Council incorporating the relevant parts of the Regulation covering medicinal products of pediatric use (Regulation (EC) № 1901/2006), European Commission (2023);
- New Regulation repealing and replacing Regulations (EC) № 726/2004 and Regulation on orphan drugs (Regulation (EC) № 141/2000) and repealing the Regulation on medicinal products for pediatric use (Regulation (EC) № 1901/2006), incorporating its relevant parts, European Commission (2023).

The proposed Directive seeks to review various key aspects of pharmaceutical regulation at EU level. Firstly, it aims to foster innovation and ensure access to medicinal products at reasonable prices, thereby establishing a balanced pharmaceutical ecosystem. Secondly, it proposes the introduction of diverse incentives associated with regulatory data protection and rewarding innovations, particularly in areas with unmet medical needs. Thirdly, the directive intends to promote greater competition by facilitating earlier market access for generic and bio- similar medicinal products. Additionally, it emphasizes the necessity for increased transparency concerning public funding of research and development activities. Furthermore, it prioritizes reducing the environmental impact of pharmaceuticals, while also advocating for a reduction in regulatory burden and the establishment of a more flexible regulatory framework to bolster innovation and competitiveness. Lastly, it outlines specific measures to improve quality and manufacturing standards in the pharmaceutical industry.

The proposed Regulation has both general and specific goals. Generally, it aims to uphold public health standards by ensuring EU patients receive high-quality, safe, and effective medicines. It also seeks to standardize the supervision and control of medicinal products across the EU, along with defining the roles of Member State authorities.

In particular, it aims to ensure timely and equitable access to affordable medicines for all EU patients. It also aims to enhance the safety of the pharmaceutical supply chain, ensuring that patients have access regardless of their location in the EU. Additionally, the regulation aims to create favorable conditions for research, development, and manufacturing of medicinal products within the EU, fostering innovation and competitiveness. Lastly, it aims to make medicines more environmentally sustainable.

Unfortunately, the access of EU citizens to advanced therapies is unequal. As yet numerous EU patients are not able to benefit from the current advances in medical science, either because they cannot afford such medicines or because they are not available as a therapeutic option, Chapman et al. (2023). Besides that the innovations are not always focused on unmet medical needs and there is a lack of developed market niches – apart from orphan drugs, there are no effective antimicrobial products to treat infectious diseases resistant to "old" antibiotics, Kohl et al. (2020), Guerriaud (2023).

The proposal for a Directive provides an option for the possibility of extending the period of data protection for medicinal products by six months from the moment of authorization if the product is designed to meet an "unmet medical need" (UMN). The regulatory proposal also formulates the criteria that the medicinal product must meet in order to be considered as such, but there is no objective definition of the unmet medical need.

The implementation of vouchers for transferrable exclusive rights for the development of new antimicrobial agents with significant clinical benefits in the fight against AMR as well as against priority pathogens recognized by the WHO is another foreseen task. On the other hand, it should be kept in mind that certain guarantees are needed in this aspect as the potential of this measure to delay the launch of generic products of other expensive innovative medicinal products (blockbusters) to which the voucher will be transferred, with an unknown financial burden on the health systems of the Member States could not be neglected. It is just the reason to look for a reasonable balance considering the fact that the outlined proposals contain a text that sets 10 as the maximum number of vouchers that could be transferred over 15 years.

The scope of the Bolar exemption is proposed to be extended to a maximum that means that research and activities conducted with the task to generate data, necessary for applying for Marketing authorization (MA), for

the process of health technologies assessment (HTA), for cost estimation and reimbursement will not be considered as infringing the intellectual property right of the original MP. It is explicitly foreseen that the permitted activities include submitting an application for a license to use, manufacture, market, supply, store, import, use and purchase of proprietary medicinal products or processes, including by third parties – suppliers and service providers. The option to sell the above-mentioned MP before the expiry date of intellectual property protection of the original is excluded from the authorized activities. In this way the patient's access to generic antibiotic medicines would be facilitated and accelerated with the aim of meeting the population`s need for antibiotics.

Other measures aiming to stimulate innovations are strengthening the early regulatory support by EMA, particularly in the process of developing innovations for the benefit of public health – the provision of scientific advice by EMA experts prior to the submission of an application for a MA, the "current" review where data are reviewed stage by stage, as soon as they become accessible.

The draft Regulation implies accelerating the assessment of promising medicines with a potential unique therapeutic advance in diagnosis, prevention, or treatment of a life-threatening, severely disabling, or serious and chronic condition by the implementation of the "current/phased review" where the data from the dossier are assessed as they become available. This will improve the quality of applications, reduce delays, and speed up the dossier approval process. The time limit for granting an authorization for use will be reduced from 210 to 180 days, and in the case of national procedures (decentralized and mutual recognition) the Commission will have 46 instead of 67 days. The so-called "clock stop" will be abolished. In the case of certain deficiencies, the regulatory authority sets a deadline for correcting the documents. After this deadline, the application will be withdrawn. The life cycle of the antimicrobial product in the environment, including the stages of manufacturing and disposal becomes a factor that must be assessed by the marketing authorization holders (MAH) when assessing the environmental risk. The goal is the reduction of the impact of the life cycle of the medicinal products on the environment and decrease of the regulatory burden, as well as provision of a flexible regulatory framework.

The proposal for a new Regulation on the development of new antimicrobial products (with significant clinical benefits in the fight against AMR and for priority pathogens recognized by the WHO) envisages introduction of vouchers for transferrable exclusive rights to the data. The draft Regulation defines the term "priority antimicrobial product" as meeting one or more of the following conditions – a novel class of antibiotics and/or a mechanism of action, totally different from that of marketed antibiotics and/or a new active substance not included in the composition of a product authorized in the EU with the capacity to combat resistant pathogens and serious life-threatening infectious diseases. This product is obligatory to be authorized under the Regulation procedure. A transferable exclusivity voucher will be granted to the pharmaceutical company that has developed the priority antimicrobial product, providing an additional year of regulatory data protection for a medicinal product of its choice. In order to receive the voucher, the company is obliged to additionally guarantee the capacity to meet the needs of the EU patients with the new antimicrobial product and to provide information on the financial sources for its development. The company receiving the voucher can use it to protect a product of its choice (extending the DP for that product) within the first four years after the DP enters into force effect or it can sell it to another company. In the event of sale, the cost of the transaction will be made public.

The introduction of the vouchers scheme creates attractive economic conditions for the development of antimicrobial products for which there is currently a very limited set of scientific research. This measure will undoubtedly delay the market launch of certain generic versions of the originals, protected by the voucher and the burden will be borne by the health systems of the Member States. That is why a maximum of 10 vouchers has been set which can be provided within 15 years. Once those years have elapsed, an assessment shall be made.

The scope of the requirements for the documents concerning the environmental risk assessment is extended, covering all stages of the life cycle of the medicinal product – from the raw materials to the finished product, with a focus on manufacturing, together with setting new goals in relation to antimicrobial resistance. Emissions and releases of antimicrobial products in the environment by the manufacturing premises can cause antimicrobial resistance (AMR). The draft Regulation obliges the MAH of antibiotics to add a leaflet on antibiotic resistance to the packaging.

Good practice from Sweden at launching newly licensed antibiotics at the national market.

Doubtless, the COVID-19 pandemics proved that infectious diseases do not recognize national borders and that investments and research are needed to accelerate the manufacturing and implementation of already existing or novel antibiotic medicinal products in all Member States. As a result of the COVID-19 pandemic, there have been global changes in economic, social and health aspects worldwide. This led to the need for accurate statistics of economic and health indicators in order to properly manage and allocate available resources, Penchev (2023). Besides actions focused on the revision of pharmaceutical legislation, in the GD HERA`s annual plan for 2023 and 2024 emphasizes actions to improve the access of the EU to newly developed antimicrobial products through a mechanism to guarantee the income of the respectiv manufacturer. The improved access to novel antibiotics has important benefits, namely the provision of treatment for multi-resistant patients that would otherwise not survive,

and the availability of better and targeted treatments to reduce the speed of resistance development.

One of the challenges for the introduction of novel antimicrobial medicinal products on the market of the EU Member States is doubtlessly the explicit will of the OLU for the respective product on the one hand, and the economic interest of the manufacturer to market its medicinal product in the financially unattractive European market such as Bulgaria, Lithuania, and Latvia.. A study, published in 2022 by Christel et al., compared newly authorized antibiotic medicinal products in the centralized procedure of the EMA and whether they were marketed in the various EU Member States. The study showed that 80%–100% of the newly licensed for use antibiotic medicinal products were marketed in countries with a high standard of living – France, Germany, Italy, Spain, Austria, and Sweden, etc. It is clearly obvious that only 20% of the antibiotic medicinal products licensed for use in the last 4 years have been marketed in Bulgaria (Fig. 2) Jansen (2022).

A good practice is the way Sweden approaches the availability of novel antibiotics on their pharmaceutical market. In 2022 Sweden implemented a new public order for antibiotics and a reimbursement model aimed at ensuring patient access to novel antibiotics despite the limited market and production capacity of the manufacturers. Under the public offer, the manufacturer had a guaranteed annual income in exchange for the timely availability of a pre-determined supply of the respective antibiotic medicinal product, BCG (2022).

Conclusion

Antimicrobial resistance has the potential to become a major international threat to human health, thus the systems of the Member States and of the European Commission should focus on early warning and detection of pathogenic microorganisms that are potentially hazardous and that could develop antibiotic resistance to the available antibiotic medicinal products. The revision of the pharmaceutical legislation leads to the conclusion that the proposed Pharmaceutical package would resolve part of the problems associated with the access to new medicinal products. On the other hand, the option of extending the exclusivity (Data protection) would provide serious grounds to consider that the introduction of generic medicines for other diseases would be delayed. It is just the point where consensus and balance should be sought between, on the one hand, satisfying the needs of EU citizens and, on the other hand, providing timely access to generic medicinal products to meet the needs of the population. The generic medicinal products, in addition to reducing public expenditure, are also a way of meeting the needs of the population for a particular medicine, since in many cases, a company holding the monopoly on the manufacture of a particular medicinal product encounters difficulties in producing it, especially in periods of high consumption. The quoted good example from Sweden as a mechanism to ensure the producers' profit is an option for the introduction of newly authorized medicinal products in financially unattractive small pharmaceutical markets, such as Bulgaria.

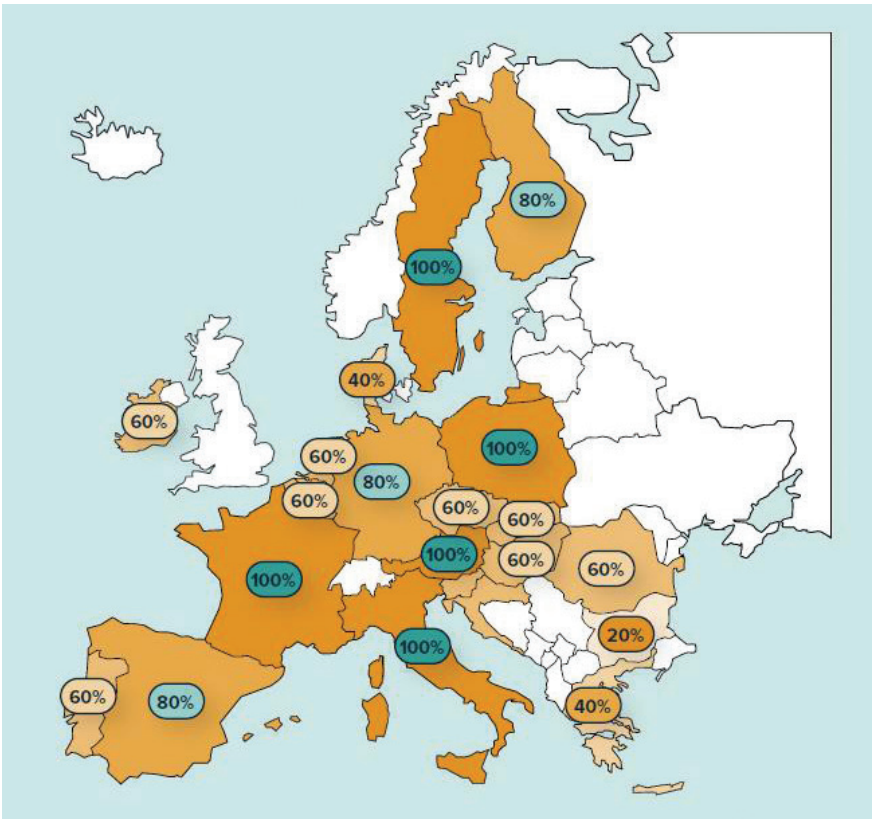

Figure 2. Availability of novel antibiotics in EU member states Jansen (2022).

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