APPROACHES REGARDING THE SUSTAINABILITY AND ENVIRONMENTAL PROTECTION IN THE PHARMACEUTICAL INDUSTRY

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***Abstract**: Sustainability and environmental protection are currently priorities of the pharmaceutical industry, a field in which more and more companies are interested in developing and implementing innovative technologies, finding sustainable solutions in the production of medicines whereby the chemical processes for producing pharmaceutical preparations are subsidiary to green chemistry. In this context, major drug manufacturers are promoting new synthesis processes involving biocatalysis reactions, the use of as few solvents as possible and a considerable reduction in the quantities and types of production waste, thus succeeding in applying the sustainability challenge on a global scale.*

Keywords: pharmaceutical industry, environment, sustainability

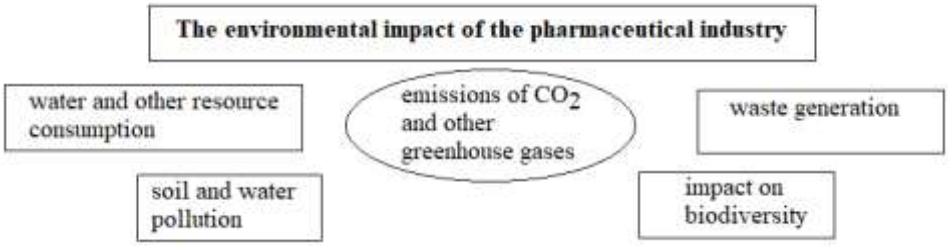
1. Introduction

The concept of sustainable development is based on the fact that development is not just about higher profits and higher standards of living for a small percentage of the population, but also about raising living standards for all. As far as the pharmaceutical industry is concerned, one side of sustainability is minimising environmental impact through the application of green technologies in drug synthesis, use of recyclable packaging, low use of single-use plastics, safely preserved pharmaceuticals and small footprint production throughout the manufacturing cycle. Thus, in today's context, the pharmaceutical industry is aligning itself with major shifts towards green chemistry and engineering in terms of raw materials used, safer solvents, less toxic to the environment, finding alternative processes and innovative green synthesis ideas, reducing operations and steps in drug synthesis and the amount of waste generated [1].

The European Parliament, in its resolution adopted on 17 December 2020, considers that a holistic approach, including all relevant stakeholders, is needed to combat pharmaceutical pollution, taking into account the whole life cycle of medicines. It points out that, in order to ensure the effectiveness of regulatory measures, it is essential that they are adopted in accordance with the precautionary principle and the principle that environmental damage should be remedied as a priority at source. It is also stressed that the polluter pays principle should be applied, primarily targeting the manufacturing process, but also encouraging better prescribing practices and responsible consumer behaviour. Issues related to the contribution of pharmaceuticals to the development of antimicrobial resistance when they enter the environment through manure dumping, water pollution or improper disposal are also raised, taking into account the need to use extended producer responsibility to reduce the negative environmental impacts of pharmaceuticals. [2]

2. The environmental impact of the pharmaceutical industry. The need to implement green technologies in drug synthesis

The pharmaceutical industry is well known for its intensive use of many petrochemical raw materials, relies on organic synthesis processes, conventional methods and technologies, and generates large amounts of waste, far in excess of that produced by other industries.



The pharmaceutical industry can have a significant impact on the environment in the following ways:

- emissions of CO_2 and other greenhouse gases. The pharmaceutical industry uses energy in the production process, which leads to greenhouse gas emissions. The transport of medicines can also generate additional emissions. Many of the pharmaceuticals we use are closely linked to the climate crisis we are facing. The pharmaceutical sector should reduce its emission intensity by around 59% from 2015 levels by 2025. The evaluation of the carbon footprint of the pharmaceutical sector shows that the emission intensity amounts to 48,55 tons of CO_2 equivalent (CO_2e) per million dollars, being 55% higher than that of the automotive sector, of 31,4 tons.
- water and other resource consumption. Production processes in the pharmaceutical industry involve the consumption of water, energy and other resources, which can have a negative impact on natural resources.
- waste generation. The production process can generate a range of wastes, including packaging and hazardous chemicals, which require responsible management and disposal.
- soil and water pollution. Water sources have come to be contaminated with measurable amounts of dangerous chemical drugs, especially antibiotics, and water treatment facilities were never designed to handle infestation with toxic pharmaceutical compounds.
- impact on biodiversity. Chemicals in pharmaceuticals can affect the diversity and health of water and soil ecosystems, with a negative effect on fauna and flora.

To minimise environmental impact, the pharmaceutical industry must adopt sustainable practices and invest in green innovations. At the same time, authorities and consumers can support and promote sustainability in this sector.

a. Waste generated by the pharmaceutical industry

An assessment of the categories of waste produced by the pharmaceutical industry highlights both the diversity and the toxic potential of some of these wastes for the environment and human health alike. Pharmaceutical activity can produce non-hazardous waste that does not endanger human health and that can be mostly recycled, such as paper/cardboard packaging waste or plastic packaging waste (stretch film, bubble wrap etc.), but also hazardous waste that poses a risk to human health and the environment and that has

one or more of the hazardous properties set out in Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives. Another category of waste is expired medicinal products and residues of chemotherapeutic substances, which may be cytotoxic, genotoxic, mutagenic, teratogenic or carcinogenic. In addition to these are infectious wastes, which are less common in pharmacies and more common in medical units, being those wastes with a "content of viable micro-organisms or their toxins known or suspected to cause disease in humans or other living organisms", according to the above-mentioned regulations. [2]

b. Contaminations in the pharmaceutical industry - health and environmental risks

The pharmaceutical industry is one of the most demanding industries in terms of hygiene standards. However, one of the major risks in the pharmaceutical industry is contamination, as its effects can be felt both on health and the environment. The effects of contamination on the environment are felt most at the aquatic level: rivers, lakes and aquifers, but soil is not excluded from these effects either. Biodiversity, drinking water and sewage systems are the first to be affected when a contamination event occurs.Conventional drug production has important consequences on the environment and water sources, not only during production, so low concentrations of drugs and metabolites have been found in rivers, lakes and coastal regions, affecting aquatic organisms (fish, benthic organisms etc.).

Although detection methods have not been developed for all pharmaceuticals entering the ecosystem, some groups have been shown to cause adverse effects on ecosystems, including increased mortality in aquatic species and changes in physiology, behaviour or reproduction.

Despite widespread concerns about the threats posed by pharmaceuticals, their release into the environment is almost unregulated. Environmental risk assessment covers only a small proportion of pharmaceuticals. There are no limits on the content of pharmaceuticals in drinking water, surface water or waste water, not even in hospital effluent, no specific regulations for the management of most waste pharmaceuticals, and no obligation to monitor or regulate pharmaceuticals in sewage sludge or manure used in agriculture. [2,3]

c. The management of expired medicines - environmental impact

Recycling medicines is an extremely important step to keep this hazardous household waste out of the environment and away from human health. Unfortunately, many of the expired ones end up being thrown away by consumers, with a large proportion ending up in the sewer or landfill. It is important to know that most medicines contain active chemicals. Once they come into contact with water or soil, they end up contaminating it, with visible effects on wildlife and the environment.

Antifungal agents (such as creams and ointments), antibiotics and anti-parasitic drugs are the most common ones to end up in the environment. Once they are consumed they can cause various ailments or resistance to the active substances in the pills can develop in humans. Exposure to these chemicals is also not only through the drinking water people consume every day, but also through residues accumulated in vegetables, dairy products, fish or meat.

Some methods of dealing with expired medicines to minimise environmental impact are: - recycling medicine packages;

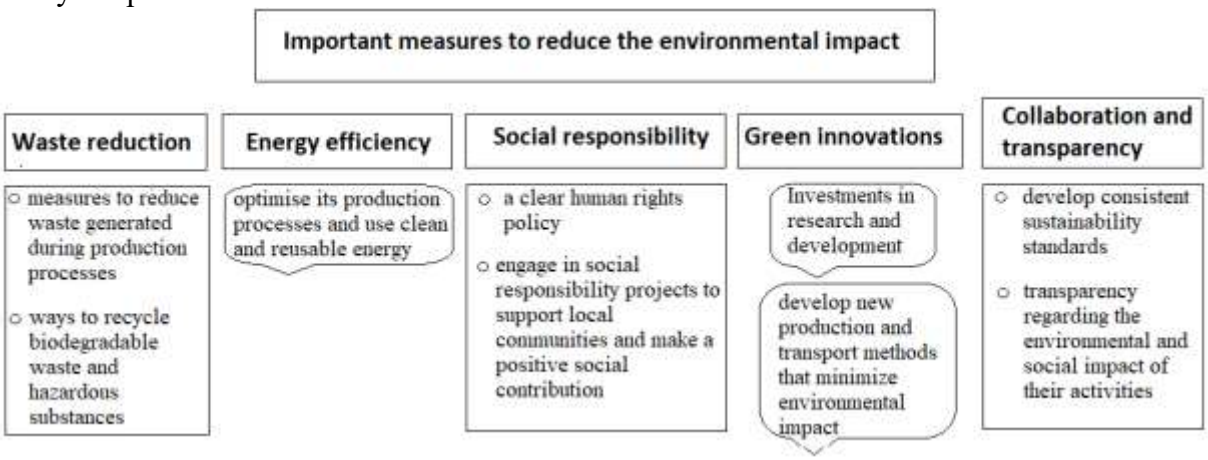
- returning medicines to pharmacies;

- proper storage of medicines and disposes of them according to safety and environmental standards;

- incineration. The method of incinerating medicines is used to destroy medicines in large quantities and minimise environmental impact by neutralising hazardous chemicals.

Like other chemical pollutants, such as pesticides, biocides or industrial chemicals, releases of pharmaceuticals into the environment need to be regulated to ensure adequate information and transparency on the environmental impact of pharmaceuticals. Adequate and reliable assessment of the environmental risks of pharmaceuticals is needed to prevent the release of pharmaceuticals into the environment throughout their life cycle and control of releases of pharmaceuticals into the environment when prevention is not feasible. [4,5]

The important measures to reduce the environmental impact of the pharmaceutical industry are presented as follows:



Sustainable solutions in the pharmaceutical industry

Green innovations in the pharmaceutical industry are innovative technologies or practices that are designed to reduce environmental impact. These can include: using renewable energy sources such as solar or wind power, improving the efficiency of production processes to reduce energy and resource consumption, using recycled or biodegradable materials in packaging for medicines, developing new transport and logistics methods that reduce carbon emissions etc. In terms of drug synthesis, there is a need to develop more precise and selective methods of chemical synthesis for drugs, which reduces waste production, the use of innovative technologies such as nanotechnologies to develop drugs with more efficient absorption in the body, thus reducing the required dose of drug. Green innovations in the pharmaceutical industry are essential to ensure sustainable production and reduce the negative environmental impact of the industry. Over the past decade, pharmaceutical manufacturers have adopted green chemistry principles to promote their environmental benefits and improve the efficiency of their manufacturing processes. In this context, many pharmaceutical companies have allocated significant sums to clinical trial research and new drug development, invested in innovative technologies, focused on the use of less toxic reagents and solvents to minimise environmental impacts, and prioritised the

reduction of solid waste in their operations. There is a great need for pharmaceutical manufacturers to implement "greener" methods, use less toxic reagents and solvents, minimise their effects and reduce industrial waste. [6]

Based on these considerations, as important solutions adopted in drug synthesis they could include:

a. The use of solvents and auxiliary agents as safe as possible

One of the principles of green chemistry concerns the use of the safest possible solvents and auxiliary agents. The use of auxiliary substances (solvents, separating agents, etc.) should be avoided wherever possible or be harmless if used at all. Another requirement of green chemistry is the replacement of hazardous volatile organic compounds with non-hazardous solvents as solvents in technological chemical processes. Environmentally friendly solvents, or so-called eco-solvents, can be categorised as solvent-free, water as solvent (environmentally safe and safe), supercritical fluids (easy and safe separation), ionic liquids (zero volatility), other environmentally acceptable solvents. In this respect halogenated organic solvents should be replaced in synthesis and technological processes, e.g. CH_2Cl_2 (dichloromethane), CCl_2CCl_2 (perchloroethylene) - possibly carcinogenic to humans; C_6H_6 (benzene) excellent solvent but genotoxic and carcinogenic to humans. [7]

Lately there has been a lot of talk about green solvents, i.e. environmentally friendly solvents or bio-solvents, which are obtained from the processing of agricultural crops. The pharmaceutical industry has initiated many studies to replace toxic solvents with solvents that are benign to human health (especially neurotoxicity and skin damage studies) and the environment. Supercritical fluids - green solvents are increasingly used in chemical processes. A supercritical fluid is formed when the temperature and pressure of the (single) substance simultaneously exceed the values corresponding to the critical point. The solvent properties of supercritical fluids are intermediate between the properties of gases and liquids, important and vital for extraction processes. Ionic liquids-green solvents are another category of solvents increasingly used in chemical processes. Ionic liquids are media in which a variety of organic and inorganic substances dissolve. Ionic liquids are organic salts (with inorganic anion and organic cation) with a melting point below 100^0C, sometimes even below room temperature. They are used instead of classical organic solvents in chemical reactions. They are attractive solvents because they are non-volatile, non-flammable, have high thermal stability and are cheap. Most of the solvents of this type are imidazole and pyridine cations as well as tetraalkylammonium or phosphonium compounds. [8]

b. Use of biocatalysts in drug synthesis

There are many successful examples in the drug manufacturing industry using biocatalysts. It can be said that biocatalysis applications in drug manufacturing has become a central issue in green chemistry with promising results. Biocatalysis is another direction in the green preparation of pharmaceuticals based on the use of enzymes to enable the transformations of different organic compounds. There are many solutions that can make a reaction that takes place in many steps with high consumption of heat and chemicals, run at room temperature, in water, very quickly with low energy consumption and easy purification process. However, some complications arise in drug synthesis, as not all chemical reactions

can take place in water. If toxic organic solvents are used, enzymes will also be affected. That's why a big challenge is to synthesise enzymes that can withstand this toxic environment or another solution would be to work with less toxic solvents. [9]

Both artificially synthesized enzymes and enzymes resident in living cells that have been isolated can participate in the biocatalysis process. Enzymes (proteins) can accelerate a reaction, decrease energy consumption, use alternative starting materials, reduce solvent use and waste production. Enzymes are biomaterials that can be degradable under environmental conditions with the advantage of reducing the number of steps in an organic reaction and the products obtained by biocatalysis do not require purification. The application of biocatalysis in the pharmaceutical industry is very low cost. Enzymes bring high selectivity but also compatibility with the aqueous environment which reduces hazards to the environment in general. [10]

Well-known pharmaceutical companies such as Pfizer have experimented for years with the use of biocatalytic reactions in drug manufacturing. In 2007, the company used enzymes as chemical biocatalysts in the basic steps of synthesis, reducing solvent use by 90% and raw materials by 50%, and significantly reducing the amount of industrial waste produced. Pfizer has done extensive research to improve the biocatalysis mechanism of Saccharomyces cerevisiae yeast. Another pharmaceutical company that has introduced green chemistry principles and biocatalysis methods into drug manufacturing is Merck. These changes brought substantial decreases in the way organic solvents are used and increased efficiency.

Biocatalysts have been used for the production of chiral intermediates needed in drug manufacturing. In living organisms, enzymes preferentially prefer one of the chiral forms of compounds in the biocatalytic conversion process. These examples are just a few of the applications of biocatalytic methods in the pharmaceutical industry that support both the principles of green chemistry and work towards a sustainable future for the chemical industry. Enzymes have high selectivity, characterized in particular by chemo-, enantio- and regioselectivity, making them effective for catalyzing a wide range of chemical transformations. Enzymes also act under adjustable pH and temperature conditions leading to the formation of high purity products. [11]

3. Conclusions

Green chemistry applied in the production of medicines covers all aspects and types of chemical processes including synthesis, catalysis, analysis, monitoring, separation and reaction conditions that reduce risk to human health and the environment and is the main way to prevent pollution. By applying green chemistry methods, the pharmaceutical industry is more efficient and thus reduces operating costs, decreases solvent consumption, reduces waste and reduces environmental impact. Modern protein analysis methods and engineering techniques have enabled new biocatalysts to be developed, adapted, designed and implemented in industrial processes. As a result, they are finding widespread application in the production of pharmaceutical intermediates. Even if it is not yet the solution to all environmental problems, green chemistry has numerous environmental and economic benefits and for these reasons the pharmaceutical industry is one of the branches that tends to adopt

most of its principles. A priority objective of the pharmaceutical industry remains the promotion of high quality, efficient and safe standards globally, thereby promoting some pharmaceuticals that are environmentally sustainable.

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