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Horizon Scanning and Early Assessment of Health Technologies for the Treatment of Orphan Diseases

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Abstract

The theoretical foundations and regulatory framework of the processes of the formation of an effective health technology assessment (HTA) system at the early stages of the life cycle of medicines are analyzed in the article. Particular attention is paid to horizon scanning (HS) and early assessment of expensive innovative drugs utilized for treating rare diseases. In order to inform policymakers, purchasers, and providers (to prioritize MT research, financial, and operational planning) or facilitate early access (by facilitating controlled dissemination of MTs), Horizon Scanning Systems, also known as "early warning and information systems, "seek to identify, filter, and prioritize new and innovative medical technologies (MTs) with significant foreseeable impacts on health, costs, society, and the healthcare system. Public and private organizations (governments, payers, healthcare systems, venture capitalists, and developers of MTs) around the world have long used formal and informal HS programs. The HS method enables proactive planning and decision-making on the use and payment of novel medications based on first evaluations of their clinical efficacy and financial impact. It is of utmost importance for rare diseases that have significant unfulfilled medical needs. Based on the review of scientific publications, analytical reports, and data from the official websites of regulatory authorities and HTA agencies, it was found that an effective system of HS, early assessments, dialogue, and managed access allows for early identification of innovative MTs that will potentially have a significant impact on healthcare. It allows us to prepare in advance for the implementation of such MTs and to rationally use limited resources and distribute risks.

Keywords: Health technology assessment, horizon scanning, early dialogue, innovative medical technologies, medicines, rare (orphan) diseases

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INTRODUCTION

Medicinal products (MPs) for the treatment of rare diseases (RDs) are always at the forefront of the latest developments and groundbreaking research. Finally, after the COVID-19 pandemic, a new "normality" has come for the global pharmaceutical industry. The pandemic has reinforced the pharmaceutical industry, as evidenced by the large number of approved innovative drugs and those under development [1].

On December 16, 2021, the UN General Assembly passed a historic resolution titled "Addressing the Challenges of Persons Living with a Rare Disease and their Families." The resolution recognizes the challenges faced by orphan patients and their families, namely inequality, social exclusion, and discrimination, due to lack of public awareness [2].

Global policy initiatives seek to realize the Sustainable Development Goals (SDGs) of the United Nations. People living with RDs are a vulnerable group that faces challenges related to various components of the SDGs. The Research Partnership will help fulfill the EU's commitment towards the UN SDGs by addressing the research needs of rare diseases. The SDGs aim to achieve universal health coverage for all individuals, regardless of their age, by 2030, and leave no one behind, with a particular focus on promoting well-being and ensuring healthy lives for all (SDG 3). The RD Partnership will also contribute towards achieving the other three SDGs. Firstly, SDG 9 (Industry, Innovation and Infrastructure) by scaling up solutions to improve the health of people living with rare diseases. Secondly, SDG 10 (Reduce Inequalities) by reducing social and health inequalities among families living with RD. The last goal, SDG 17 (Partnerships for the Goals), aims to lessen the fragmentation of resources, information, and skills in RD research by encouraging global collaboration [3]. The 2000 EU Regulation on Orphan Medicinal Products (OMPs) provides legal backing and regulation for EU policies and initiatives in the areas of healthcare and research. Even among the scientific community, there was little interest in OMPs prior to the passage of this legislation. The Commission Communication on Rare Diseases, which was approved in 2008, the Council Recommendation on an action in the field of rare diseases, and the Directive on the application of patients' rights in cross-border healthcare furthered the significant political measures. The EU Framework Programmes (FP) for Research and Innovation (R&I) have prioritized rare disease research for a long time The establishment of the International Rare Disease Research Consortium (IRDiRC) in 2011 and the effective implementation of joint transnational research requests through succeeding ERANets, along with the successful coordination of national research funding schemes, serve as evidence of this. The European Joint Program on Rare Diseases (EJP RD) was launched in 2019, with a duration of 2023, and stands as an important milestone in Europe. This program is a stunning example of coordinated Member State cooperation. From the perspective of European research policy, the Partnership on Rare Diseases will contribute to the ambitious goal of the Horizon Europe Partnerships (2021–2027) to become a key instrument for the implementation of the Horizon Europe program to maximize its impact, and will make a significant contribution to the achievement of EU policy priorities for 2019–2024 and beyond. The Partnership on Rare Diseases seeks to establish collaborations and missions for EU research and innovation as major participants in the European Research Area (ERA) [4, 5]. In this context, health technology assessment (HTA) at the early stages of the life cycle and horizon scanning (HS) aimed at identifying new and promising medical technologies (MTs) that could potentially impact healthcare becomes increasingly important.

It is estimated that up to 36 million people in the EU member states suffer from rare diseases, of which there are about 6000 [6]. 80% of rare diseases are of genetic origin, 70% manifest in childhood and have a severe course and lead to disability. Due to the small population, limited evidence base, difficulties with diagnosis, and lack of available MTs, orphan patients often do not receive proper treatment. The situation results in a rise of medical needs that remain unfulfilled. Accordingly, improving patient access to diagnostics, information, and care has been recognized as a political priority in most countries, and appropriate measures have been taken at the national and global level [7].

According to an analytical report by Evaluate Pharma, the orphan drug market is growing twice as fast as the conventional drug market, with an average annual growth rate of 12% in 2021–2024. According to forecasts, by 2026, sales of orphan drugs will account for 20% of all prescription drug sales [8, 9].

At the same time, access to orphan medicines in the EU is still not ideal and equitable. Only 37% of these medicines are affordable, compared to 46% of all medicines. Additionally, the level of access to orphan medicines differs significantly across Europe, ranging from almost no access in Lithuania to almost complete access in Germany. The situation is further complicated by significant delays between the time a drug is authorized for marketing and when patients can access it. On average, this delay is 636 days for orphan drugs (compared to 511 days for other drugs) [7].

LITERATURE REVIEW

The international experience of conducting research on HS and organizational and regulatory aspects of this issue is covered in scientific publications, analytical materials, etc. In particular, S. Vogler analyzed the state of national and interstate HS systems in European countries [10, 11], N. Grössmann, S. Wolf, K. Rosian, C. Wild consider the use of HS and early HTA for "pre-reimbursement" [12], i.e., coverage decision-making.

Features of the organization of the HS system in Italy are described by J. Ivanovic, G. Capone, L. Raffaelli, M. Marangi, and G. Pistritto [13, 14]. Future trends and technologies from the cooperation of the European Medicines Agency in the field of HS are considered in the publication of V. Vignali, P. A. Hines, A. G. Cruz, B. Ziętek, R. Herold [15]. Recommendations for the development of potential for HTA conducting in low- and middle-income countries, in particular, regarding the selection and prioritization of topics for evaluation, are presented by Norwegian scientists V. Lauvrak, J. Bidonde, E. F. Peacocke [16]. The involvement of patients and the public in early information and warning activities (based on the example from the UK) is discussed in the article by S. Simpson, A. Cook, and K. Miles [17]. The methodology and features of HS, as well as analytical data, are described in numerous guidelines and reports from different countries [18, 19].

The purpose of the article is to study current approaches to HS and early evaluation of innovative MTs, in particular for the treatment of rare diseases that currently have no available treatment technologies.

METHODS AND MATERIALS

Analysis, systematization and generalization of data from scientific publications, analytical reports, information from official websites of regulatory authorities (FDA, EMA), HTA and HS agencies, and the Orphanet network.

RESEARCH RESULTS AND DISCUSSION

Based on an extensive review of scientific publications and official websites of organizations involved in HTA at different stages of the life cycle and performing regulatory functions in the areas of marketing authorization, pricing and reimbursement (P&R), three main areas were identified that could potentially affect the development of innovations to meet unmet needs: HS and early HTAs; early dialogue between manufacturers, regulators, and HTA experts; and Managed Entry Agreements (MEAs). The key role is assigned to an effective HS system, the so-called "early warning system", which allows for identifying innovative MTs with the potential to impact healthcare. HS is conducted before (or immediately after) market entry/regulatory approval, usually 1–3 years before the MT becomes available in the healthcare system (Figure.1).

This system disseminates information in a timely manner to enable appropriate decision-making (including resource allocation) and identifies the need for further research. HS is considered as the first stage of HTA.

It is worth noting that innovative MTs from the HS perspective can be classified as follows: completely new MTs (new chemicals, devices, procedures); existing MTs used for a new group of patients, new indications; significant incremental changes in existing MTs that may have a significant impact on clinical outcomes, healthcare systems or human resources.

In 2011, the International Rare Diseases Research Consortium (IRDiRC), which includes 60 organizations worldwide, was established to develop 1000 new treatments for diseases that do not have approved MTs and treatment protocols. Recently, there has been a trend towards expanding cooperation between stakeholders in the field of evidence collection, conducting HTA and risk sharing from the early stages of clinical trials to post-registration monitoring. At the same time, the heterogeneity of the regulatory framework and practice of HTAs complicates the market access environment.

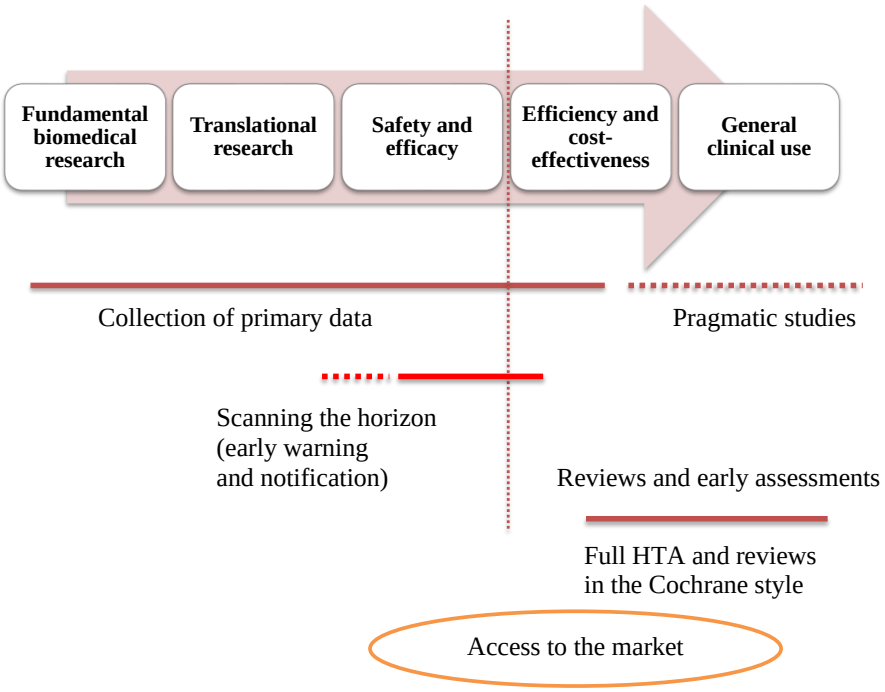

Figure 1. The role of horizon scanning in HTA [19].

Analysis of the results of the European Medicines Agency (EMA) activities on the approval of medicinal products showed that in 2022, 89 new medicinal products were approved. Out of these, 48 contain new active substances, 8 are biosimilars, 23 are equivalents, and 10 are hybrid medicines that contain known active substances and have been approved based on the informed consent procedure. Among the medicinal products containing new active substances authorized by the EMA, the highest number (37.5% in total) belong to the categories of anticancer drugs and immunomodulators used for treating solid tumors such as lung, prostate, and liver cancer, blood cancers like myeloma, lymphoma, and leukemia, and autoimmune diseases. This is followed by antimicrobials for systemic use, drugs for treating gastrointestinal (GI) tract diseases, metabolic diseases, and drugs for the nervous system [20].

It is worth noting that medicines with orphan drug status in the EU benefit from 10 years of market exclusivity if they receive marketing authorization and continue to meet the criteria (no alternative MTs for the treatment of RD). In the United States, orphan drug status entitles sponsors to tax benefits for qualified clinical trials, exemption from subscription fees, and 7 years of market exclusivity after approval [20].

In 2022, the EMA received 269 applications for Orphan Drug Designation (ODD). The EMA Committee for Orphan Medicinal Products (COMP) granted orphan status to 176 medicinal products, which allowed them to benefit from the incentives provided by the EU Orphan Drug Fram ework Program, 77 medicinal products were withdrawn, and 2 received negative decisions from COMP. In 2022, the EMA authorized 20 orphan drugs that contain new active substances, with 5 of them being advanced therapies, particularly gene therapy. The EMA also granted positive decisions for 91 new indications for 67 already registered drugs, mainly for anticancer and immunomodulatory drugs. As of early 2023, the EMA was evaluating 92 new medicines, including 61 new active substances, 28 of which are orphan drugs, 17 equivalents, and 14 biosimilars. Antineoplastic drugs are the most numerous (25), followed by immunosuppressants (14) and nervous system drugs (6). A total of 111 medicinal products have been approved for the PRIME program, which supports promising medicinal products at the early stages of development that are of high interest to healthcare organizations and intended for patients with unmet needs. Most of these products are advanced therapies, and the field of oncology has the highest representation [20, 21].

In 2023, the European Orphan Medicines Registry included 136 medicines that received the appropriate status, in particular for new rare indications. Among them are 7 medicinal products for the treatment of pancreatic cancer, 5 for amyotrophic lateral sclerosis, 4 for Duchenne muscular dystrophy, 4 for sarcoma, 4 for glioma, 3 for ovarian cancer, 3 for Leigh syndrome (including cannabidiol), 3 for Alport syndrome, sarcoidosis – 2, sickle cell anemia – 2, limb-girdle muscular dystrophy (LGMD) – 3, perinatal asphyxia – 2 (melatonin), spinal cord injury – 2, treatment of Huntington's disease – 2, narcolepsy (sodium oxybate) – 2, myelofibrosis – 2, etc. It is worth noting that some medicines were approved for several indications. For example, Fosmanogepix is indicated for the treatment of scedosporiasis, mucormycosis, fusarium, and lomentosporiasis; efzofitimod is indicated for the treatment of systemic scleroderma, sarcoidosis [21].

According to the latest reports, the Food and Drug Administration (FDA) had a total of 55 new drugs approved through the Center for Drug Evaluation and Research (CDER) in the year 2023. Out of these, 28 drugs (51%) were classified as “orphan drugs” (ODD) as they were designed to treat RD. Some of these drugs are used for treating paroxysmal nocturnal hemoglobinuria (Fabhalta™ – iptacopan), activated phosphoinositide 3-kinase δ syndrome (Joenja™ – leniolisib), CHAPLE syndrome (Veopoz™ – pozelimab), hereditary transthyretin-mediated amyloidosis (Wainua™ – eplontersen), Friedreich's ataxia (Skyclarys™ – omaveloxolone), Rett syndrome (Daybue™, trofinetide), and other diseases. Additionally, three enzyme drugs were approved for the replacement therapy of rare genetic pathologies: Lamzede™ (velmanase alfa) for alpha-mannosidosis, Elfabrio™ (pegunigalsidase alfa) for Fabry disease, and Pombiliti™ (cipaglucosidase alfa) for late-onset Pompe disease. The FDA also approved the marketing of birch triterpenes (Filsuvez™) in the form of a gel for topical use to treat incomplete wounds in epidermolysis bullosa, which is a rare and currently incurable disease.

HS is conducted by a small number of agencies around the world. There are several interagency and intergovernmental cooperation programs in Europe and other regions. The international network EuroScan has been operating since 1997 for 20 years as an association of regulatory authorities of European countries (Canada, Denmark, Spain, Canada, the Netherlands, Sweden, Switzerland, and the UK), and in 2017 – expanded its geography and acquired the status of a non-profit scientific association, whose members were both government agencies, scientific organizations and individuals, in 2020 transformed into the International Health Tech Scan (i-HTS), remains the main global forum for the exchange and development of methods for early detection and preliminary assessment of new and obsolete MTs. Currently, attention is focused on interventions with high potential in the following focus areas: Alzheimer's disease and other dementias, cancer and cardiovascular diseases, mental and behavioral disorders, and RD. Due to COVID-19, the range of HS has been expanded.

Evidence-based uncertainty at the time of marketing authorization often makes it difficult to evaluate and negotiate prices and reimbursement for orphan medicines. The problem of small populations is exacerbated for ATMPs considering the relatively short duration of trials compared to the expected long-term effects of these MTs. There is a consensus to mitigate uncertainty through adaptive pathways and greater use of real-world evidence from routine practice (RWE). It has the potential to complement the understanding of the efficacy of medicines, optimal clinical use, outcomes in specific target populations, and the expected impact on the budget. For instance, conditional access allows for increased accessibility of medicines for patients, while RWE is generated to further assess clinical outcomes and value. The collection of RWEs requires collaboration between many stakeholders, especially for RDs that affect a small number of patients in a single country.

The Innovative Medicines Initiative (IMI) was created for interstate cooperation on the production and use of RWE. On 23rd February 2021, the European Commission proposed a Single Basic Act (SBA) to establish various joint ventures under Horizon Europe. One of these joint ventures is the Innovative Health Initiative (IHI). The resolution was adopted on November 19, 2021. The purpose of the IHI is to help create a pan-European ecosystem of research and innovation in healthcare that will

help transform scientific knowledge into real innovations in the field of prevention, diagnosis, treatment that are safe, effective, and cost-efficient. IHI contributes to several European policies, including the European Cancer Plan, the New Industrial Strategy, and the Pharmaceutical Strategy for Europe. IHI brings together different stakeholders in joint projects aimed at combating diseases that place a high burden on patients and society. Five organizations—COCIR, EFPIA, EuropaBio, MedTech Europe, and Vaccines Europe—have cooperated with IHI.

In order to deliver fast and accurate information on the usage, safety, and efficacy of medications, including vaccines, from actual databases of healthcare institutions throughout the EU, the European Medicines Regulatory Network (EMRN) and the European Medicines Agency (EMA) launched the establishment of a clearinghouse in 2021. The Data Analysis and Real-World Interrogation Network (DARWIN EU®) is the former name of the center.

The GetReal Institute is based on the positive experience of previous IMI projects: The GetReal Project (2013-2017) and The GetReal Initiative (2018-2021), and brings together a wide range of stakeholders (regulators, manufacturers, patients, clinicians, payers and policymakers, scientists, healthcare organizations, etc.) to promote the sustainable development and implementation of tools, methods and best practices in the creation and use of RWE for better decision-making in the healthcare sector.

RWE4Decisions is a multi-stakeholder initiative established by the Belgian National Institute for Health and Disability Insurance (INAMI-RIZIV), which includes politicians, healthcare providers, payers, regulators, physicians, patient groups, researchers, registry owners, data analysts, industry and academic experts. It brings together stakeholders to agree on what real-world data can be collected for highly innovative MTs – when, by whom, and how – to produce RWEs to inform decision-making by health systems (healthcare providers/payers), physicians, and patients. In addition, the European Digital Health and the European Rare Disease Research Coordination and Support Action (ERICA), as well as European Reference Networks (ERNs), have the potential to facilitate the coordination of RWE collection.

The challenges associated with developing medicines for small populations (e.g., lack of disease knowledge, difficulty generating robust evidence, higher development costs per patient, higher prices required to ensure sufficient profitability) mean that most orphan medicines have a harder time demonstrating added benefit and/or value for money based on conventional criteria (rigorous clinical benefit and cost-effectiveness assessments, such as quality-adjusted life-year cost estimates).

Traditional HTA methods need to be adapted to RDs, mainly by providing flexibility for evidence uncertainty and introducing context-specific willingness-to-pay thresholds. Many countries include or plan to introduce process adaptations for RDs (e.g., increased thresholds for ultra-rare diseases in Norway and Sweden, simplified evidence requirements, and automatic additional benefits in Germany).

The flexibility of P&R processes also means refraining from restrictions on reimbursement within the EMA labeling to avoid denying access to patients who may benefit from the therapy. Wherever possible, all eligible patients within an authorized EMA label should be considered for reimbursement, given the difficulty of obtaining evidence across all subgroups of patients with RDs.

Regulation (EU) 2021/2282 on HTA provides for joint activities in the EU Member States on clinical assessments, scientific advice, HS, and further voluntary cooperation. Joint Clinical Assessments (JCAs) will be mandatory and will focus on the evaluation of clinical evidence, while economic considerations will remain country-specific. The first phase of implementation (2025-2027) will focus on oncology medicines and advanced therapeutic medicines (ATMPs), including those for the treatment of RDs.

CONCLUSIONS

The goal of HS systems, also known as "early warning and information systems," is to find, screen out, and rank new and creative MTs that have major, predictable effects on health, expenses, society, and the healthcare system. This information is then used to either prioritize health research, financial planning, and operational planning for policymakers, purchasers, and healthcare providers, or to enable early access through the controlled distribution of MTs. Public and private organizations (governments, payers, healthcare systems, venture capitalists, and medical technology developers) around the world have long used formal and informal HS programs. Proactive planning and decision-making about the use and reimbursement of new medications are made possible by the HS system and are based on initial assessments of the financial impact and clinical efficacy. It is of utmost importance for rare diseases that have significant unfulfilled medical needs.

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