The Horizon Scanning System at The Italian Medicines Agency

Michele Marangi[1], Jelena Ivanovic[1] and Giuseppa Pistritto[2]

[1] Analisys and Forecasting Activities Office, Department of Economic Strategy of Pharmaceutical Products, Italian Medicines Agency, Rome, Italy
[2] Centralized Procedures Office, Department of Economic Strategy of Pharmaceutical Products, Italian Medicines Agency, Via del Tritone, 181-00187 Rome, Italy

The new era of medical innovation is a great opportunity for healthcare; but it poses new challenges for affordability of healthcare systems. To enable timely implementation of value-based clinical care and payment approaches, it is important to look beyond usual timescales to inform decision makers about forthcoming disruptive technologies early. Horizon scanning could represent an efficient tool in support of decision making and rational use of available resources. Different horizon scanning programmes exist in Europe and there is a need for further international cooperation between competent authorities. In relation to this, the present review aims to highlight the importance of early information availability and illustrates the Italian Medicines Agency Horizon Scanning System in the context of the European regulatory network.

Introduction

With >7000 medicines in development globally (of these potential first-in-class medicines are ~74%) [1], the new era of medical innovation is a great opportunity for healthcare progress; but it also represents a new challenge for affordability and sustainability of National Health Systems (NHSs). Considering this, in the coming years, many 'game-changing' medicines will be launched in different therapeutic areas. The pressures are not only financial because the ultimate goal is to ensure that patients will have timely access to innovation to promote public health. Looking ahead, beyond the usual timescales and across disciplinary borders, seeking alternative sources of information to inform decision makers about forthcoming therapeutic options early is mandatory to achieve this goal. The present review aims to highlight the importance of early information availability for decision making concerning innovative and disruptive technologies. At the same time, it illustrates the Italian Medicines Agency (AIFA) pharmaceutical Horizon Scanning System (HSS) in the context of the EU's regulatory Horizon Scanning (HS) network.

Corresponding author: Marangi, M. (m.marangi@aifa.gov.it)

A role of early information availability for regulatory decision making and timely access to innovation

Based on learning principles, it is believed that the availability of relevant information on a real-time basis and in different forms can accelerate decision making, by identifying problems or opportunities quickly [2]. Improving the support for decision making through information products (e.g., different reports) for operational and strategic or tactical decisions is one of the most important goals of business intelligence that is also applicable to the pharmaceutical regulatory framework [3,4]. Regulatory systems should strive toward positive changes in innovation strategies and should enable distinguishing of products on the basis of clinically, socially and economically relevant criteria [5]. Different regulatory tools [e.g., different authorisation paths, scientific advice procedures as well as the European Medicines Agency (EMA) Priority Medicine Scheme (PRIME)] have recently been developed with the aim to promote timely access to new medicines in EU and are based on early information availability and anticipated assessment. However, these tools might not be sufficient to fully address increasing healthcare requests when treatment for unmet clinical needs is urgently warranted. Thus, regulators should be informed in a timely manner about potentially disruptive or transformational products. Moreover, implementation of explicit filtration

https://doi.org/10.1016/j.drudis.2019.04.010

and prioritisation criteria through HS application is important because payers are not motivated to allocate resources for medicines with limited or absent clinical needs [6].

The Health Technology Assessment International (HTAi) Global Policy Forum [7] has pointed out HS in terms of framework development and efficient complementary tools for programming healthcare resources. HS is defined as the systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society [8]. After identification, it also includes selection and filtration, prioritisation, assessment and information dissemination activities. The timing of HS can vary depending on the purpose of HS activity. HTA HS is typically performed close to the time of application for marketing authorisation (MA): 2–3 years before MA, whereas other types of HS could be performed earlier (5–10 years or earlier). This mainly focuses on platforms (e.g., novel manufacturing technologies or new classes of medicines).

European approach to HS of pharmaceuticals with focus on regulatory frameworks

Early HS activities and systems were developed in the 1990s and, since then, several institutions in Europe and worldwide have been acting in the field of Early Awareness and Alert (EAA). In 1999, the International Network EuroScan [9] was established to enhance the exchange of information on new and emerging health technologies among members of public institutions and academic areas working on the topic. In Italy, two EAA systems: the Italian Horizon Scanning Project (IHSP) focusing on medicines [10] and the Agenas-HS with a focus on non-pharmaceuticals (i.e., devices) [11], were established between 2006 and 2008 and they mainly operate at national and regional levels. European HSS mainly aims at identifying, filtering and prioritising new and emerging health technologies that could have a significant impact on healthcare systems (HCS), in order to inform policymakers, purchasers and healthcare providers about these technologies and/or to facilitate early access to these medicines [12]. Indeed, some of the existing national HSS are developed to support HTA as well as price definition and negotiation activities [13].

To identify existing regulatory-body-based HSS in different EU countries, the search was performed among the websites of other regulatory bodies and academic institutions as well as projects and organisations considered to be involved in HS activities. Additionally, an open web source and literature (MEDLINE OR PubMed) search was performed to identify relevant public organisations in Europe involved in HS activities for pharmaceuticals by using the following key words: 'Horizon Scanning', 'pharmaceuticals', 'medicines', 'regulatory', 'Europe'. The most active, developed and national HS systems (or alliances) pertinent to pharmaceutical National Competent Authorities (NCAs) or regulatory frameworks are illustrated in Table 1. The systems have many common points in processes concerning different phases of HS (Table 1) and most of them take 2–3 years to scan health technologies [14]. Despite similarities in approaches, some differences can be recognised in terms of purpose, size, resource, operational level, mandate, stakeholder involvement, end-users, output and organisational embedding (Table 1) [15]. Additionally, prioritisation of health technologies for further assessment is a well-established approach among international HTA bodies but differences are reported in prioritisation criteria applied in different HSS, although healthcare costs have been recognised as the most predominant criterion together with organisational consequences [13]. Some possible challenges that are faced by national HSS (e.g., limited resources, data and appropriate expertise availability, engagement of external experts) could be overcome by cooperation and work-sharing at an international level, whereas some differences in priorities as well as sharing of confidential information are identified as possible barriers for cooperation. In recent years, EU institutions and bodies have promoted different incentives and alliances to ensure EU member states cooperate in this area [16–24]. The HS activities of the EMA, another important pillar in EU pharmaceutical systems, are based on their Regulatory Science Observatory, which pools together information from internal established groups (e.g., the innovation task force and business pipeline) and, together with the Scientific Committees, identifies expected submissions and new and emerging areas in science, technology and therapeutic approaches.

The goals of HSS at AIFA

AIFA, unlike the majority of other medicines agencies in Europe, is responsible for national MA and price, reimbursement and innovation definition. The Italian agency relies on three main tools to reduce budget impact of novel therapies: price negotiations, cap on specific drug expenditures and performance-based schemes [25]. Definition of prices and reimbursement conditions of medicines reimbursed by the health service are established, after the MA is granted, through negotiation between AIFA and the pharmaceutical companies, in accordance with national laws [26].

In this context, to support the programming and prioritisation of economic resources and to promote early access, HSS of AIFA aims to identify and to inform decisionmakers early on about new medicines and new therapeutic indications of marketed medicines with potentially meaningful impact on an NHS. The AIFA decision-making body and HS end-users, beside the Director General, are the AIFA Prices and Reimbursement Committee (CPR, *Comitato Prezzi e Rimborso*), which carries out the activity of price negotiation with pharmaceutical companies of medicinal products reimbursed by the health service, and the Technical Scientific Committee (CTS, *Comissione Tecnico Scientifica*), which assesses MAs, provides classification for reimbursement and defines the innovation level of a new medicine. Currently, the evaluation of the innovations in Italy is based on three fundamental elements: therapeutic need, added therapeutic value and quality of clinical studies [27].

How does HSS at AIFA work?

AIFA HS concerns medicines in development under EMA evaluation for an MA with expected opinion in the next 36 months (including PRIME programme medicines). It is focused on a systematic collection of information and structured in five consecutive phases: identification, selection and prioritisation, assessment, dissemination of information and evaluation of outcomes. In addition, monitoring of performance is done for all phases of the process (Fig. 1). All outputs are archived in a common cloud-based platform accessible to registered end-users.

Identification

The most valuable sources of information for AIFA HSS (Fig. 1) are the EMA documents (e.g., information on medicines under scien-

TABLE 1

Overview of selected publicly funded regulatory oriented Horizon Scanning Systems (HSS) for pharmaceuticals in Europe

HSS organization and/or website	Aim and type	HS database	Stakeholders and company involvement	Process and expert involvement Identification (I), selection (S), prioritisation (P), assessment (A), dissemination (D) or other	Outputs and the main users
The Netherlands[a] [13,33]					
Ministry of Health, Welfare and Sport (VWS)[a] from 2014 https://www.government.nl/ministries/ministry-of-health-welfare-and-sport	Price negotiations/appraisal process; evaluation of MP financial risk with thresholds	No publicly accessible database	Professional, healthcare providers, insurers and patient associations	A qualitative scoring system for three well-defined cost criteria: a 'traffic-light' approach, P by use of implicit criteria, clinical experts (external)	Meetings, information sharing on a new expensive drugs, indication expansion and duration of patents with internal (HTA) and external [National Health Care Institute, healthcare providers (HCP), insurances, patients] users
Sweden [13,31]					
Swedish Agency for HTA and Assessment of Social Services (SBU) from 2007 https://www.sbu.se/en/	Managed products introduction, support of HTA and long-term planning	Database accessible by working group members and representatives from the county councils	The working group meetings with members from the four counties and meetings with companies	I, S, P, A, D I, P: predefined criteria, quarterly schedule Experts affiliated with the regional Drug and Therapeutic Committees (DTCs)	Decision on managed or non-managed introduction such as prioritisation of high impact products. List of prioritised medicines; quarterly newsletters; early assessment reports (6 months before the authorisation) for the county councils (New Therapies Council)
UK [6,13]					
The NIHR Innovation Observatory (NIHR IO) from 2017 http://www.io.nihr.ac.uk/for-the-public/ HS activities performed in collaboration with NICE	Managed products introduction, support of HTA and support for prescribing	Innovation Observatory and UK PharmaScan	HCP, local prescribing committees and organisations, patients, companies, regional centres	I, S: NIHR S, P: additional selection and prioritisation by NICE A: preliminary technology briefs – NIHR IO A: final briefs (non-commercially sensitive information) – NICE Internal and external experts	Preliminary and final technology briefs/reports (information on all new medicines 24–30 months before the launch, AR 20 months before the launch; AR for new indications 15 months before the launch), pipeline analysis reports (trends in clinical innovation for the next 5–10 years) for NHS, NICE, UK Government, commissioners, providers of NHS services (including NHS budget holders), healthcare professionals and those involved in planning and assessment of potential impact of new drugs on the local health economy

TABLE 1 (*Continued*)

HSS organization and/or website	Aim and type	HS database	Stakeholders and company involvement	Process and expert involvement Identification (I), selection (S), prioritisation (P), assessment (A), dissemination (D) or other	Outputs and the main users
National Health Service (NHS)/UK Medicines Information (UKMi) from 2014 (in current form) http://www.ukmi.nhs.uk/ The UKMi Horizon Scanning and Medicines Evaluation (HSME) working group https://www.sps.nhs.uk/networks/ukmi-horizon-scanning-and-medicines-evaluation-working-group/	The managed entry of new drugs into the NHS, assistance in developing medicines management policies and information to prescribing decisions when a product has been launched; it encompasses early horizon scanning intelligence through to evaluations of medicines once marketed	The UKMi website for registered NHS users and UK PharmaScan: it links to reviews produced by UKMi, London New Drugs Group, the National Institute for Health and Clinical Excellence (NICE), Medicines & Prescribing Centre, UK national appraisal committee work and regulatory documents from the EMA and FDA	NHS Commissioners, medicines management leads, directors of Public Health, chief executives Department of Health, formulary or directorate pharmacists, senior pharmacy managers, finance directors, NICE implementation leads, prescribing committee members	I, S, P, A, D	Information for early HS: UKMi's New Drugs Online (NDO) database (contains information about drugs in clinical development through to launch), a monthly NDO Newsletter Information for planning: Prescribing Outlook: New Medicines section of the SPS website (catalogue of new medicinal products 12 to 18 months before launch), prescribing outlook – national developments (national targets that could have budgetary implications over the next 12 to 18 months), prescribing outlook – cost calculator, new medicines newsletter. The users are NHS staff with budget setting, prescribing planning and medicines management responsibilities
NHS England Specialized Service https://www.england.nhs.uk/participation/get-involved/how/specialised-services/ The Horizons (http://horizonsnhs.com/about/) and Sustainable Improvement Teams (https://www.england.nhs.uk/sustainableimprovement/)	Evidence-based, quality improvement support that helps to deliver NHS England's priorities and achieve the objectives set out in the Five Year Forward View; support to the wider NHS system to make transformational improvement; input to Scottish Medicines Consortium appraisals	Improvement Knowledge Hub and UK PharmaScan: it archives improvement knowledge, information and tools to support the delivery of sustainable service improvement from the NHS organisations	The health and care system, the wider public sector and publicly funded healthcare systems	–	Improvement Knowledge Hub, Change Model and the Leading Large Scale Change: A Practical Guide Among users there are: NHS Institute for Innovation and Improvement, National Cancer Action Team, National End of Life Care Programme, NHS Diabetes and Kidney Care
Northern Ireland Health and Social Care Board http://www.hscboard.hscni.net/	Planning for commissioning processes	UK PharmaScan	HCP, patients, commissioners, companies	–	Briefings for presentation to commissioners to facilitate forward planning
MHRA – the Horizon Scanning Programme https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency	Identification of new and emerging areas of scientific and technological research and development (including digital developments) such as new medical products and devices in the pipeline and general health trends	UK PharmaScan	Internal Horizon Scanning Working Group – HSWG, companies	Signal on new/innovative technologies detection	Input and advice, assessment reports for decisionmakers/management, product reviewers and scientists

TABLE 1 (*Continued*)

HSS organization and/or website	Aim and type	HS database	Stakeholders and company involvement	Process and expert involvement Identification (I), selection (S), prioritisation (P), assessment (A), dissemination (D) or other	Outputs and the main users
The All Wales Medicines Strategy Group (AWMSG) from 2002 http://www.awmsg.org/ Complementary to the National Horizon Scanning Centre	Price negotiations/appraisal process; identification of the medicines that requires appraisal by AWMSG. Advise on the potential impact for the NHS	UK PharmaScan	NHS clinicians, pharmacists, healthcare professionals, academics, health economists and patient advocates. Meetings and data submission by pharmaceutical companies	I, S, P, A, D P: no implicit criteria	The meetings and minutes of all AWMSG meetings are made public A confidential report for therapeutics advisory committees detailing the products that are expected to be appraised during the following year
The Scottish Medicines Consortium (SMC) from 2002 https://www.scottishmedicines.org.uk/	Managed products introduction and financial risk identification to support financial and service planning by the Scottish Health Boards for new medicines expected to come to market over the next financial year	UK PharmaScan	Pharmacists, health service researchers, management accountants, clinical and the pharmaceutical industry	I, S, P, A, D P: implicit criteria Process described in guidance document available at: https://www.scottishmedicines.org.uk/about-us/horizon-scanning/	The annual HS report (Forward Look, each October) on medicines with the potential to have a moderate to high impact on the drug budget and/or significant implications for service delivery. A set of financial spreadsheets on all new medicines expected to reach the market within the next calendar year. Templates with cost estimates for budgeting purposes to be used in the local health boards. Guidance on horizon scanning. Access to the website is only given to named health board personnel, including those involved in HS or financial planning, upon receipt of a signed confidentiality agreement
Spain [34]					
AETS – Agencia de Evaluación de Tecnologias Sanitarias in coordination with the Spanish Regional HTA Agencies and Units in the Spanish HTA Network from 1994 http://www.isciii.es/ISCIII/es/general/index.shtml	Evaluation of the medical, social, ethical and economic impact of the use of health technologies; HTA advising NHS authorities; supporting systematic reviews on health technologies at the national level	–	–	P, A: health technologies are prioritised for assessment Engagement internal and external reviews	AETS reports, advice and scientific and technical support for Spanish Ministry of Economy, Industry & Competitiveness, the Ministry of Health and to the National Health System (NHS)

TABLE 1 (*Continued*)

HSS organization and/or website	Aim and type	HS database	Stakeholders and company involvement	Process and expert involvement Identification (I), selection (S), prioritisation (P), assessment (A), dissemination (D) or other	Outputs and the main users
The Basque Office for Health Technology Assessment, Basque Country (OSTEBA) http://www.osakidetza.euskadi.eus/r85-pkoste01/en/ The SorTek Program of Basque Office for Health Technology Assessment, Basque Country from 1992	Identification, prioritization and early warning and assessment of new and emerging health technologies in support of medical practice and the organization of healthcare delivery; The coordinator of the Spanish Network for New and Emerging Technologies	–	Collaboration with different stakeholders including HCP, epidemiology research units and the Drug Information Centre of the Basque Country	Health technologies are divided in: hot topics, probable rapid dissemination technologies (less than a year), diffusion probably higher than a year and these considered emerging issues in the local area Advisory committees provide scientific support and identify priorities in a structured way Reports are performed by internal and external experts	The program creates a 'red alert' for emerging technologies that can affect clinical practice; full assessment reports, mini HTA reports; methodological guides, clinical practices guidelines (GPG); a newsletter 'Osteba Berriak' and training activities. The main users are the Ministry for Health and the Basque Health Service-Osakidetza for policy making and by hospitals, clinicians and private care providers
Switzerland					
Swissmedic https://www.swissmedic.ch/swissmedic/de/home.html	Information necessary to support innovation/for managers and decisionmakers; identification of innovative medicines	–	Companies are not involved	S, P, A, D P: use prioritisation criteria Internal experts	Assessment reports for decisionmakers; Internal Horizon Scanning Guideline
Norway [19]					
Norwegian Institute of Public Health (NIPHNO) from 2015 https://www.fhi.no/en/ Norwegian horizon scanning unit (NIPH)	Support of HTA, identification of technologies of special interest	The process relies on reliable data from external sources and open access international early assessments	Documents submission by companies	I, S, P, A, D	A final alert is produced with recommendations for HTA and serves as a proposal to the system. The drafts of alerts are published online at the Norwegian Medicines Agency (NoMA)
Ireland[a]					
The Health Products Regulatory Authority (HPRA)[a] https://www.hpra.ie/ The Horizon Scanning and Scientific Affairs Group Denmark	To support innovation while appropriately regulating innovative and disruptive products and technologies	–	Different stakeholders including companies	I, S, P, A, D P: use prioritisation criteria Engagement of internal experts	Assessment reports Internal Horizon Scanning Guideline U: decision-makers, internal staff

TABLE 1 (*Continued*)

HSS organization and/or website	Aim and type	HS database	Stakeholders and company involvement	Process and expert involvement Identification (I), selection (S), prioritisation (P), assessment (A), dissemination (D) or other	Outputs and the main users
Amgros from 2017 http://www.amgros.dk/en/	Support of HTA, prediction of therapeutic changes and costs, a full overview of new pharmaceuticals, indications and pharmaceutical forms (2–3 years before marketing authorisation in Denmark)	–	Different stakeholders including pipeline meetings with companies and information requests	I, P, A, D	Amgros lists and reports: overviews and list of new medicines; overviews and list of extensions of indication for internal (procurement and optimising of the tendering process) and external users (input for the Medicine Council, drug committees and other healthcare professionals) and for negotiations between Danish Regions and the Ministry of Finance
Italy					
Italian Medicines Agency (AIFA) from 2018 http://www.aifa.gov.it/content/ufficio-attivit%C3%A0-di-analisi-e-previsione	to support HTA, to identify medicinal products with potential impact (clinical and economic) on NHS	No	Involvement of companies and other stakeholders is programmed	I, S, P, A, D P: use prioritization criteria Involvement of internal experts	Different types of HS reports (12 months, 36 months, prioritisation and single medicine reports) for internal use of AIFA – Director General, decision-makers, HTA Department
BeNeLuxA + Ireland[a] [13]					
BeNeLuxA (Belgium, The Netherlands, Luxemburg and Austria, Ireland) from 2015 http://www.beneluxa.org/ The new initiative – The International Horizon Scanning Initiative (IHSI) is based on countries (European and non-European) 2017; operational in 2018	Identification of important pharmaceutical innovations before they reach the market; insight in expected costs, timely decision making and (joint) price negotiations; creation of a permanent HSS that can support countries and institutions in policy planning and their decision making on the reimbursement of new pharmaceuticals	Database collecting data on all pharmaceuticals in development from Phase I; all originator pharmaceuticals in development from Phase II/Phase III; medicines with a potential high impact; pharmaceuticals that have failed or are withdrawn from FDA/EMA registration procedures; registered medicinals; patent data for pharmaceutical products; all generics and biosimilars coming to market	Different stakeholders and EMA	I, S, P Impact assessed by use of a validated methodology	Advice for timely decision making and (joint) price negotiations; publication of list of products that might have a large impact on our health systems; a study on HS that underlines the importance of a broad cooperation Users are national decisionmakers/policy makers

illustrates a selection of some HSS and does not aim to provide comprehensive review of HSS in Europe. The selection is also based on data availability from open sources.

[a] Members of The International Horizon Scanning Initiative and BeNeLuxA.

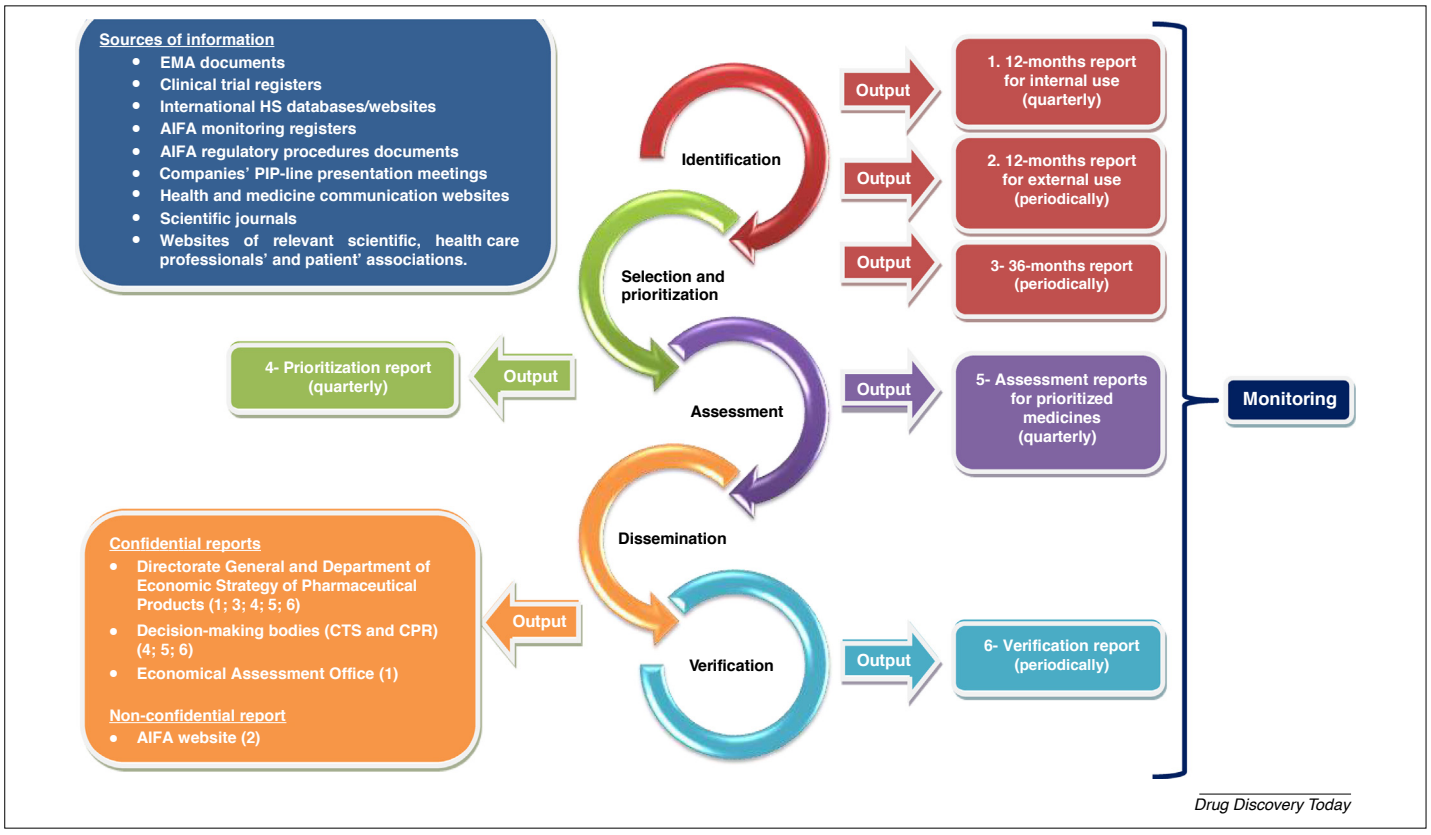

FIGURE 1

Horizon Scanning System (HSS) of the Italian Medicines Agency (AIFA): phases and the main outputs. HSS of AIFA is structured in five consecutive phases: identification, selection and prioritisation, assessment, dissemination and verification; monitoring of performance is transversally performed for all phases of HSS. The main outputs (reports) produced in different phases of the HS process are included in different coloured boxes. AIFA HSS sources of information are listed in the light-blue box. All these sources are consulted on regular bases during the entire process of HS. The orange box includes information about end-users of AIFA HS information. Type of output that is provided for different end-users is specified in the same box as well.

tific advice, centralised authorisation, orphan designations and PRIME programme procedures). Additionally, clinical trial registers (e.g., clinicaltrials.gov, The Italian National Monitoring Centre for Clinical Trials – OsSC, WHO International Clinical Trials Registry Platform – ICTRP), international HS databases and websites (e.g., FDA website and Weekly Digest Bulletin, NHS Observatory, EMA, Health Canada, ICER – Institute for Clinical and economic Review, AHRQ – the Agency for Healthcare Research and Quality, etc.), AIFA new medicinal products monitoring registers and regulatory procedures documents, company PIP-line presentation meetings as well as news, health and medicine communication websites (e.g., Science Daily, Medpage Today, Pharma Times, Orphanet, UptoDate, MedScape, etc.) are all useful sources of information. The scientific journal websites are consulted on a regular basis, such as websites of relevant scientific, healthcare professional (HCP) and patient associations.

The identification phase is considered completed when information on identified new medicines and new therapeutic indications is provided in the '12-months report' (as quarterly bulletins) or '36-months report' (periodically issued bulletins). The 12-months report analyses a period of four consecutive quarters and includes cumulative and medicine-specific data on medicines that could receive the MA by the EMA in the next 12 months (ATC classification, name, active substance, orphan designation status, the date of MA procedure beginning, therapeutic indication and alternatives, date of expected opinion of the EMA) relative to new active substance, biosimilar, equivalent and new therapeutic indications of already authorised medicines. The report includes the same type of information for EMA PRIME programme medicines as well (those having a high public health interest and intended for patients with unmet medical needs). The 36-months report provides cumulative and medicine-specific information (see above) on all medicines that could receive the EMA opinion in the upcoming three consecutive years and on the most represented therapeutic areas and indications.

Selection and prioritisation

From medicines included in the 12-months identification report, additionally selected in accordance to selection criteria (Fig. 2), the prioritisation activity aims to highlight those that could have a relevant clinical and economic impact on NHSs. The selected medicines then enter the prioritisation process.

Prioritisation tool

The medicines are prioritised through a scoring prioritisation tool that allows calculation of a final prioritisation score for each medicine. Scoring is based on the six main predefined criteria (Table 2) in the 'clinical and economic impact' domain. Domains and prioritisation criteria were selected in consensus with the

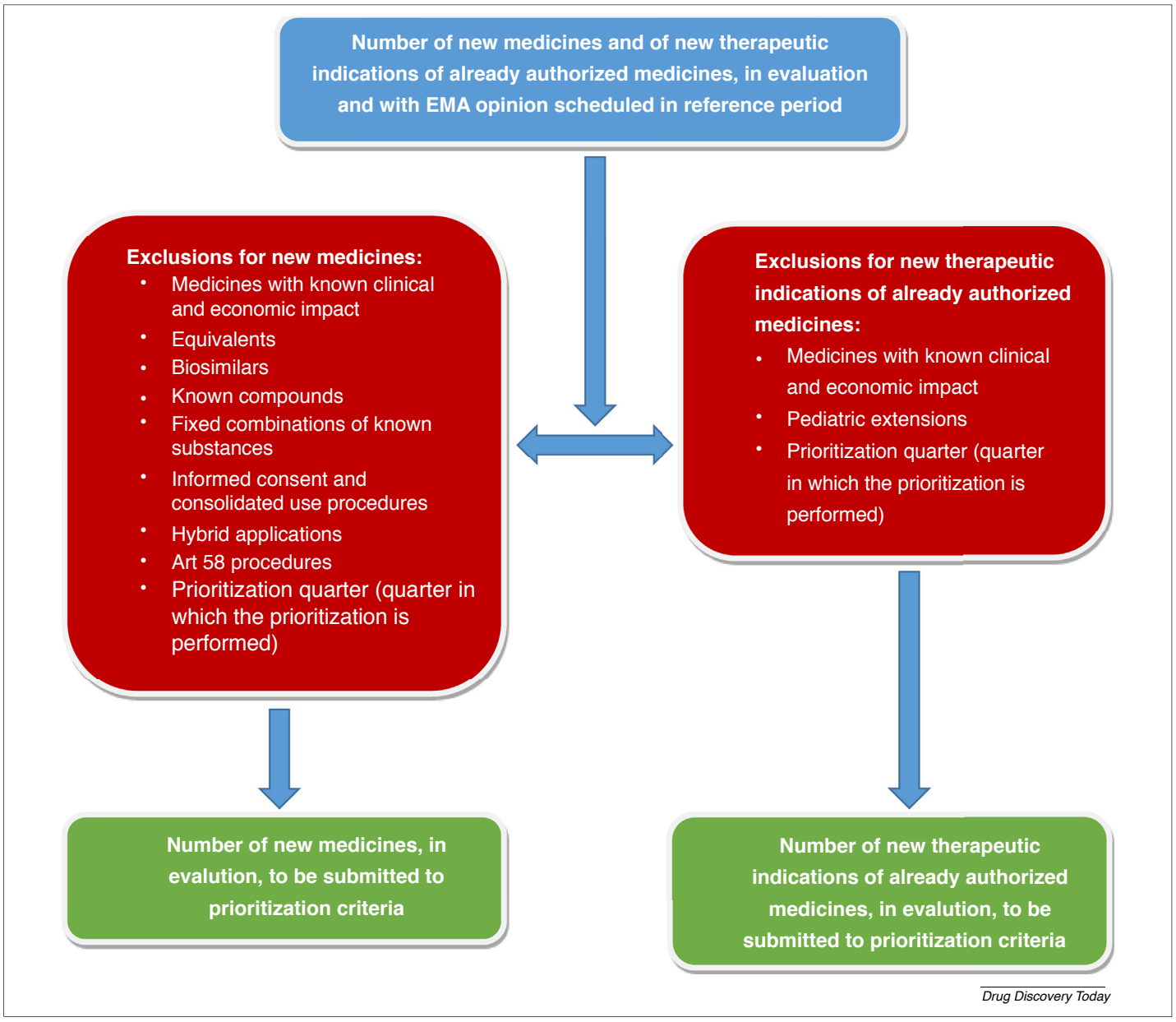

FIGURE 2

Selection criteria for exclusion of medicinal products not eligible for prioritisation. During the selection phase, medicines found at the identification stage are considered and, by applying pre-set criteria, those of major relevance to the Italian healthcare system (HCS) are selected to ensure the best use of available resources and targeted evaluation in later phases. Further restriction to medicines of special interest is obtained subsequently by use of predefined prioritisation criteria (prioritisation tool).

internal experts (the criteria are specific to AIFA and might not be automatically applicable to other contexts) and the same group of experts has participated in the tool validation by testing 50 medicines from various therapeutic areas. Testing involved comparing results from structured 'tool'-based prioritisation against estimation of the product impact without a tool. The latest was based on AIFA clinical and scientific expert opinions, who were asked to group these medicines into three different categories on the basis of their estimation of the potential clinical, organisational and economic impact. Considering that results of two types of prioritisation matched in >95% of cases and the products considered to have a major impact were all prioritised by the tool (and collocation of non- prioritized medicines in the other two categories was the same for both methods), it was considered as a sufficient proof for internal adoption and use of the tool.

All criteria included in the tool have the same attributed value. According to the importance attributed, disease and organisational impact criteria are scored on a scale of 0 to 3 points whereas all other criteria are scored on a scale of 0 to 4 points (therapeutic need, potential therapeutic value, estimation of patient number to be treated and estimation of treatment annual cost; Table 2). In addition, through the 'regulatory aspects' domain, it is possible to attribute additional scores for the regulatory status of the medicine (orphan designation, 5 points), the quality of clinical studies when data are still incomplete and preliminary (limited only to availability of the Phase III double-blind randomised clinical trials,

TABLE 2

The prioritisation criteria that are applied to medicines identified through the application of selection criteria and assessment report structure

Prioritisation criteria		
Clinical and economic impact criteria	**Levels definition**	**Explanation**
Disease impact	High mortality **3** High morbidity and/or disability **2** Significant compromising of quality of life **1** None of previous **0**	Disease for which the medicine is used, produce high mortality, morbidity, disability or significantly compromised the quality of life
Therapeutic need	The highest (absence of treatment options for a specific indication) **4** Important (available therapeutic options for a specific indication are without impact on clinically relevant and validated outcomes for a specific disease) **3** Moderate (available therapeutic options for a specific indication are with limited clinical impact evaluated on clinically relevant outcomes and/or with non determinate or unsatisfactory safety profile) **2** Scars (one or more therapeutic options are available for a specific indication with high clinical impact evaluated on clinically relevant outcomes and with favourable safety profile) **1** Absent (available therapeutic options for a specific indication are able to modify natural history of disease and have favourable safety profile) **0**	Therapeutic need is dependent on the pharmaceutical treatment availability for the proposed indication and specifies how much the introduction of new therapy is necessary for appropriate addressing of the patient population clinical need. All available therapeutic alternatives that have received at least the positive opinion of EMA and these included in the AIFA list based on national law concerning off-label use (law 648/96) [35] should be considered
Potential therapeutic value	The highest (greater efficacy demonstrated on clinically relevant outcomes with respect to available therapeutic options – when available. The medicine is curative or at least it significantly modifies natural history of disease) **4** Important (greater efficacy demonstrated on clinically relevant outcomes, the medicine is able to decrease a risk for disability or potentially fatal complications, or has better benefit:risk ratio (R:B) with respect to the available alternatives, or ability to avoid use of clinical procedures at a high risk for patients. The medicine modifies natural history of disease in specific subpopulations, or induces clinically relevant benefit, for example in terms of quality of life and disease-free periods with respect to available therapeutic alternatives) **3** Moderate (moderate major efficacy or efficacy demonstrated in specific subpopulations or on surrogate endpoints and with limited effects concerning quality of life) **2** Scars (greater efficacy demonstrated evaluating non clinically relevant outcomes or demonstrated efficacy is limited. Minor advantages and benefits, for example better favourable rout of administration – with respect to available alternatives) **1** Absent (no additional advantages or benefits are recognised with respect to available alternatives) **0**	The potential therapeutic value is determined on the bases of the entity of the clinical benefit brought by the new medicine in comparison to the available therapeutic alternatives for the same indication. All available therapeutic alternatives that have received at least the positive opinion of EMA and are included in the AIFA list based on national law concerning off-label use (law 648/96) [35] should be considered
Organisational impact	High (a need for complete reorganisation of the care structure) **3** Medium (additional tests/procedures/interventions highly specialised with and with high impact on care system) **2** Low (additional tests/procedures/interventions respect routine practice and with moderate impact) **1** None (routine tests) **0**	Necessity of additional organisational changes/ instruments/test/procedures for the clinical practice (the way care is provided)
Number of patients to be treated	High ($\geq$ 50 000 people) **4** Medium-high ($\geq$ 10 000 $<$ 50 000 people) **3** Medium ($\geq$ 1000 $<$ 10 000 people) **2** Low ($\geq$ 100 $<$ 1 000 people) **1** Very low ($<$ 100 people) **0**	Estimation of the number of patients to be treated in the national context

TABLE 2 (*Continued*)

Prioritisation criteria		
Clinical and economic impact criteria	**Levels definition**	**Explanation**
Estimation of treatment cost per year	Very high (≥ 300K) **4** High (≥ 150K < 300K) **3** Medium-high (≥ 50K < 150K) **2** Medium (≥ 10K < 50K) **1** Low (< 10K) **0**	Estimation of treatment cost for the first year of treatment

Regulatory status criteria	**Explanation**
Orphan drug designation (+5 points)	Orphan drug designation by EMA (because of special interest in this group of technologies)
ATMP (+5 points)	Advanced therapy medical product (because of special interest in this group of technologies)
Quality of evidence (+2 points)	Availability of Phase III randomised, double-blind clinical trials (RCT)

	Assessment report structure
The predefined sections of assessment reports	- General information and regulatory status - Disease impact - Epidemiological data - Mechanism of action - Posology - Available therapies for the proposed indication (authorised, off label use [28]) - Innovation and/or advantages - Main clinical studies (efficacy and safety) and scientific uncertainties - Other indications for the same medicine in development - The way care is provided/organisational impact - Ethical, social, legal, political and cultural impact - Final considerations (including clinical and economic relevance) - References

The applied criteria are specific to AIFA and might not be automatically applicable to other contexts.

intended as recognition of good scientific evidence for the prioritisation purpose, 2 points) and for advanced therapy medical products (ATMPs, 5 points), owing to the enormous impact of ATMPs on healthcare (the number of further applications will increase in the future) and socioethical relevance of orphan medicines. Once the data are entered, the tool automatically performs all the calculations. The sum of weighted scores of individual criteria within the 'clinical and economic impact' domain is calculated on the basis of the 100 score and the bonus of 5 or 2 points from the 'regulatory aspects' domain can be added.

When the final scores are obtained through the prioritisation tool, medicines are categorised into three different categories (cut-offs have been defined by internal expert working groups) and the outcomes of prioritisation are reported in the prioritisation report:

- Medicines to be included in the prioritisation list (to be assessed): score ≥65 points.
- Medicines to be monitored: score ≥50 and <65 points.
- Medicines not included in the previous categories: score <50.

Hence, the main output of this phase is a prioritisation report (provided quarterly) that includes a ranking-list of medicines (based on obtained prioritisation scores) that will be used for identification of medicines for assessment. No data entered into the tool are stored on the web, which guarantees the total confidentiality of any data introduced. During the prioritisation phase internal clinical experts are involved to facilitate the process of prioritisation in terms of time and resource allocation and expenditure assuring and minimisation of conflicts of interest [28].

Assessment

For prioritised medicines and for some medicines placed into the list for monitoring (cases of particular interest), single medicine reports focused on clinical therapeutic value are provided quarterly. Medicines admitted to the PRIME programme, addressing a high therapeutic need and value recognised by the EMA, are not included in the prioritisation process but it could be decided on the case by case basis to provide directly assessment reports.

The predefined sections of assessment reports are reported in Table 2. The availability of those reports is 18–24 months before the national market entry of medicine (AIFA Committee opinions). More-structured economical evaluation is performed by a competent office of AIFA, when the EMA opinion is available to provide a more accurate estimation of economic impact. The information is, however, available before medicine entry to the Italian market (12 months before) and the planning of resource allocation for pharmaceuticals. During the assessment phase, before the final assessment report is made available, an internal peer-review check for accuracy and consistency of all assessment reports is performed.

Evaluation of the quality and impact outcomes

An analysis of the decision-making process, by verifying the outcomes of the HS system and these of health policy decisions, is useful to measure the HS activities impact [29]. To compare HS outcomes (estimation of therapeutic need, therapeutic value, number of potential users of a medicinal product and its annual

treatment cost) with those resulting from the negotiation process, an ex-post-analysis should be performed which is structured in two steps:

- Accuracy of forecasting and provided information: a score-based HS prioritisation system was adopted to enable quantitative 'verification'. Analysis against final committee decisions by use of a 'pre- and post-score system' will be performed for prioritised medicines such as the calculation of level of concordance between two evaluations. Usually, when evaluating information products (e.g., reports, information delivery and forecasting information), accuracy, effectiveness and context, coverage can be measured by using quantitative data. Considering similarity between HS prioritisation criteria and the AIFA Committee scoring system for clinical and economic impact definition (e.g., innovativeness level and price), the matching of attributed scores could be easily performed. Possible differences and the reasons will be analysed as well.
- Evaluation of level of satisfaction, effectiveness and utility: anonymous format questionnaires and interviews to the end-users will be performed to enquire about accessibility (e.g., the way and format of provided information, coverage or acquisition) and utility (which information, when, where and for what type of decisions was of major relevance).

The results of impact evaluation, in the form of a report provided periodically, will be used for improvements in the proposed model.

Dissemination of information

All information collected through the HSS is analysed and organised in previously mentioned reports and shared with the main end-users of HS information: reports containing confidential information with Directorate General and Department of Economic Strategy of Pharmaceutical Products and AIFA decision-making bodies (CTS and CPR) and non-confidential reports are shared publicly trough the AIFA website (Fig. 1).

Monitoring

Standard operating procedures regarding definition of the process and HSS activities have been developed. Monitoring has been introduced to evaluate key performance indicators such as the time dedicated to activities, possible obstacles to the activities and workloads. Corrective measures are foreseen in case some abnormalities are detected (e.g., time dedicated to different activities, adjustments, etc.).

Concluding remarks

Innovative disease-modifying therapies offer great hope and benefits to patients, their families, caregivers, healthcare systems and society. Providing timely, transparent and programmed access to innovation is one of the main goals of a modern HCS; however, foreseeing technological changes and the development of organised early information-based decision-making processes is a challenging task [14]. Disruptive technologies should be promptly detected and evaluated; the first toolkit for the identification and assessment of new and emerging health technologies was developed by the EuroScan International Network in 2009 and recently updated [30]. The main stages involved in early-awareness and alert HS processes continue to be identification, filtration, prioritisation and assessment; different approaches can be taken at each of these stages for development of HS systems. The BeNeLuxA collaboration showed that the successful implementation of the joint HSS could increase the negotiating power of a single NCA and that drug policy might become more demand-driven, for example by giving priority to those pharmaceutical products that meet an unmet medical need [8]. Similarly, the outputs from Swedish HSS have been recognised as important for programming and prioritisation of resource allocations [31].

Our experience highlights the importance of development and implementation of methodological approaches for HS activities and shows how the prioritisation tools, based on scored predefined criteria, could be sensible enough to allow for discrimination of different categories of medicines with various characteristics and effects on HCS. The implementation in routine regulatory practice could support early identification of medicinal products of special interest and allow for anticipated programming of resources by an NHS. In addition, the example of the Italian HS process could be informative for other NCAs planning to introduce it in their regulatory systems. However, there are some limitations in our approach that could be mentioned together with adjustments that have been adopted. One of these issues is related to efficiency of data search methodology. In the absence of automatic tools for data searching and a direct involvement of developers, the activities dedicated to data acquisition require time and resources. With implementation of additional strategies for improvement of data quality and access (e.g., early and structured dialogue with companies and other stakeholders), the AIFA HS process could be further improved. Digital and analytical tools to facilitate active scanning of the scientific literature and other data sources appeared to still be limited. The *TIM Edge*, a tool developed by the European Commission Research Centre in collaboration with the EMA, is one of the successful examples [32] and it puts together various datasets to track emerging technologies (e.g., patents, scientific publications, other datasets, news from the media, etc.).

The second issue concerns consistency in assessor evaluation owing to possible subjectivity in score attribution despite utilisation of predefined criteria. To improve consistency in prioritisation and evaluation, internal expert meetings are regularly organised for discussion and sharing of final outcomes of prioritisation and peer-review is performed for all assessment reports. Finally, in relation to accuracy of HS previsions, it is clear that it depends on data availability (stage of development of medicinal product) at the time point of prioritisation and assessment. Additional data that will be collected in the advanced phases of development could potentially change the initial evaluations. Thanks to the periodic evaluation of the HS outcomes, the impact and the accuracy of early information will be evaluated and could be improved if necessary.

In conclusion, a robust HSS at the country level is needed to help HCS plan and prepare for innovation. However, the perception of the value and the risk of a technology could be different between regulators, health professionals and patients. Therefore, it is important that regulators collaborate and engage with HCPs and

patients for an effective identification of high value medicines. No less important is international collaboration at the regulatory authority level for time-saving, duplication-avoiding and best-practice-based learning on HS methodologies and activities for improvement of the system.

Acknowledgements

The authors thank colleagues from the Department of Economic Strategy of Pharmaceutical Products of the Italian Medicines Agency for contribution during the HSS development and support in different activities of process.

References

1 Pharmaceutical Research and Manufacturers of America (2016) *Biopharmaceutical Research Industry Profile*. PhRMA, Washington, DC Available at: https://www.bms.com/assets/bms/us/en-us/pdf/biopharmaceutical-research-industry-2016-profile.pdf
2 Leidner, D.E. *et al.* (1995) The impact of executive information systems on organizational design, intelligence, and decision making. *Organ. Sci.* 6, 645–664
3 Isik, O. *et al.* (2011) Business intelligence (BI) success and the role of BI capabilities. *Int. Syst. Accounting Finance Manag.* 18, 161–176
4 Popovič, A. *et al.* (2012) Towards business intelligence systems success: effects of maturity and culture on analytical decision making. *Dec. Support Syst.* 54, 729–773
5 Mittra, J. *et al.* (2011) The future of pharmaceutical innovation: new challenges and opportunities. *IPT Online* 36, 32–34
6 Oortwijn, W. *et al.* (2018) Facing the dynamics of future innovation: the role of HTA, industry and health system in scanning the horizon. HTAi Global Policy Forum 2018 Background Paper. *Int. J. Technol. Assess. Health Care* . http://dx.doi.org/10.1017/S0266462318000363
7 The HTAi Global Policy Forum 2017. Available at: https://htai.org/policy-forum/global-policy-forum/.
8 The Health Technology Assessment (HTA) Glossary. Horizon Scanning. Available at: http://htaglossary.net/horizon+scanning.
9 The International Information Network on new or emerging medicines – EuroScan International Network. Available at: https://www.euroscan-network.global/index.php/en/about.
10 Joppi, R. *et al.* (2009) The Italian Horizon Scanning Project. *Eur. J. Clin. Pharmacol.* 65, 775–781
11 Agenzia Nazionale per I Servizi Sanitari Nazionali – AGENAS. Available at: http://www.agenas.it/aree-tematiche/hta-health-technology-assessment/hs-horizon-scanning.
12 Simpson, S. *et al.* (2014) A toolkit for the identification and assessment of new and emerging health technologies. In *Technical Report*. Available at: http://epapers.bham.ac.uk/2120/1/EuroScan_Methods_Toolkit_October_2014_FINAL_CC_added.pdf
13 Lepage-Nefkens, I. *et al.* (2017) Horizon scanning for pharmaceuticals: proposal for the BeNeLuxA collaboration. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). *KCE Rep.* 283 D/2017/10.273/15
14 OECD (2017) *New Health Technologies: Managing Access, Value and Sustainability*. Available at: http://www.oecd-ilibrary.org/social-issues-migration-health/managing-new-technologies-in-health-care_9789264266438-en2017
15 EUNetHTA (2017) *Horizon Scanning, Topic Identification, Selection and Prioritization for European Cooperation on HTA – Draft Recommendations*. Available at: https://www.eunethta.eu/wp-content/uploads/2018/07/180629-Horizon-scanning-recommendations_draft-5_forconsultation.pdf2017
16 The Interest Group (IG). Disinvestment and Early Awareness (DEA). Available at: https://htai.org/interest-groups/disinvestment-and-early-awareness/.
17 The Nordic Pharmaceutical Forum – NLF. Available at: http://www.amgros.dk/en/areas/nordic-collaboration/.
18 European Council. Note from the General Secretariat of the Council. Furthering a member state driven voluntary cooperation to support access to medicines. Brussels, 27 January 2017. Available at: http://data.consilium.europa.eu/doc/document/ST-5170-2017-INIT/en/pdfhttp://data.consilium.europa.eu/doc/document/ST-14574-2017-INIT/en/pdf.
19 WHO Regional Office for Europe. Division of Health Systems and Public Health. Health Technologies and Pharmaceuticals Programme. Report from technical working meeting on access to new medicines – joint horizon scanning and strategic negotiations opportunities. Available at: http://apps.who.int/medicinedocs/documents/s23295en/s23295en.pdf.
20 Valletta Declaration. Available at: https://www.eu2017.mt/Documents/Declarations/Declaration_EuroMed%20Cooperation%20in%20Research%20and%20Innovation.pdf.
21 Sofia Declaration of the EU-Western Balkans summit. Available at: https://www.consilium.europa.eu/en/press/press-releases/2018/05/17/sofia-declaration-of-the-eu-western-balkans-summit/.
22 Grubert, N. (2018) *A landmark for international collaboration on HTA and pharmaceutical pricing*. Available at:2018 In: https://www.linkedin.com/pulse/landmark-international-collaboration-hta-pricing-neil-grubert
23 FINOSE, a Nordic cooperation. Available at: https://www.tlv.se/in-english/international-collaboration/finose—a-nordic-cooperation.html.
24 EU. Proposal for a Regulation of the European parliament and of the Council on Health Technology Assessment and Amending Directive 2011/24/EU. Available at: https://ec.europa.eu/health/technology_assessment/eu_cooperation_en.
25 Flume, M. *et al.* (2018) Approaches to manage 'affordability' of high budget impact medicines in key EU countries. *J. Mark. Access Health Policy* 6, 1478539
26 Individuazione dei criteri per la contrattazione del prezzo dei farmaci. Available at: http://www.gazzettaufficiale.it/eli/id/2001/03/28/001A3188/sg.
27 Criteri per La Classificazione Dei Farmaci Innovativi e Dei Farmaci Oncologici. Available at: http://www.aifa.gov.it/sites/default/files/Allegato1_criteri_valutazione_innovativit%C3%A0.pdf
28 Regolamento per la disciplina dei conflitti di interesse all'interno dell'Agenzia Italiana del Farmaco. Available at: http://www.agenziafarmaco.gov.it/sites/default/files/regolamento_disciplina_conflitto_interesse.pdf.
29 Marchetti, M. and Cicchetti, A. (2015) *La valutazione delle tecnologie sanitarie*. Available at: http://www.sifoweb.it/biblioteca-sifo/altre-edizioni/2082-la-valutazione-delle-tecnologie-sanitarie-una-guida-pratica-per-le-aziende-sanitarie.html2015
30 EuroScan International Network. A toolkit for the identification and assessment of new and emerging health technologies. Available at: http://epapers.bham.ac.uk/2120/1/EuroScan_Methods_Toolkit_October_2014_FINAL_CC_added.pdf.
31 Eriksson, I. *et al.* (2017) The Early Awareness and Alert System in Sweden: history and current status. *Front. Pharmacol.* 8, 674
32 EU Commission Joint Research Centre. TIM Edge Info. Available at:.
33 Government of Netherlands. Complete set of regulations for securing the affordability and accessibility of expensive medicines. Available at: https://www.government.nl/documents/publications/2016/03/07/appendix-2-complete-set-of-regulations-for-securing-the-affordability-and-accessibility-of-expensive-medicines.
34 Basque Office for Health Technology Assessment. Available at: http://www.euskadi.eus/web01-a2ikeost/en/https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/horizon-scan_research-2013.pdf.
35 Italian Medicines Agency – AIFA. Lists of medicines used on basis of national off-label use law (law 648/96). Available at: http://www.aifa.gov.it/content/legge-64896.