Pharmacological Research 197 (2023) 106967

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Clinical pharmacology facing the real-world setting: Pharmacovigilance, pharmacoepidemiology and the economic evaluation of drugs

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ARTICLE INFO

Keywords:
Pharmacovigilance
Adverse drug reaction
Pharmacoepidemiology
Effectiveness
Efficiency
Real world evidence
Pharmacoeconomics
Health technology assessment

ABSTRACT

Traditionally, clinical pharmacology has focused its activities on drug-organism interaction, from an individual or collective perspective. Drug efficacy assessment by performing randomized clinical trials and analysis of drug use in clinical practice by carrying out drug utilization studies have also been other areas of interest. From now on, Clinical pharmacology should move from the analysis of the drug-individual interaction to the analysis of the drug-individual-society interaction. It should also analyze the clinical and economic consequences of the use of drugs in the conditions of normal clinical practice, beyond clinical trials. The current exponential technological development that facilitates the analysis of real-life data offers us a golden opportunity to move to all these other areas of interest. This review describes the role that clinical pharmacology has played at the beginning and during the evolution of pharmacovigilance, pharmacoepidemiology and economic drug evaluations in Spain. In addition, the challenges that clinical pharmacology is going to face in the following years in these three areas are going to be outlined too.

1. Introduction

Clinical pharmacology's main objective is to individualize therapeutic decisions. Broadly speaking, pharmacology analyzes what the human organism does with the drug (pharmacokinetics) and what the drug does to the organism (pharmacodynamics). Classically, clinical pharmacology has focused on this drug-organism interaction, from an individual or collective perspective. The evaluation of pharmacological effects, through randomized clinical trials, has been the cornerstone of the specialty since its creation. However, the ideal conditions in which clinical trials are carried out are far from the conditions in which drugs are used in normal clinical practice. For this reason, currently, the regulatory approval of a drug cannot be the end point of the process of evaluating its effects, but only the beginning of the process that must necessarily consider all the implications of the use of drugs in the real life. Fig. 1 summarizes the main trends in drug evaluation that have emerged in recent years. Through the conduct of clinical trials, "Evidence-Based Medicine" focuses on the analysis of efficacy, generating useful information for regulators. Nevertheless, it is necessary to complete this information with the development of "Comparative Effectiveness Research" and "Health Technology Assessment", whose objective is to generate relevant information also for clinicians and payors.

Clinical pharmacology should move from the exclusive analysis of the drug-individual interaction to the analysis of the drug-individual-society interaction. The study of pharmacokinetics in society involves analyzing the elements that determine the process of incorporation, distribution, and elimination of a drug from the time it is added to the therapeutic arsenal until it is no longer used. Drug utilization studies are the paradigm of this pharmacokinetics in society, an activity that clinical pharmacology has embraced since its inception. However, the specialty must also study social pharmacodynamics, that is, the analysis of the clinical and economic consequences of the use of drugs in the conditions of normal clinical practice, beyond clinical trials. The growing

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https://doi.org/10.1016/j.phrs.2023.106967
Received 10 August 2023; Received in revised form 15 October 2023; Accepted 18 October 2023
Available online 20 October 2023

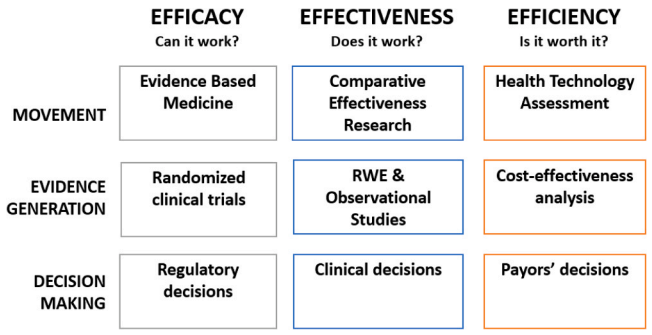

Fig. 1. Methods to assess the efficacy, effectiveness and efficiency in the decision-making process. RWE: Real world evidence.

regulatory trend towards conditional drug approvals [1], or the exponential development of a technology that facilitates the analysis of real-life data [2], should provide a new impetus to a specialty that aims to achieve a more rational use of drugs through the study of the best evidence generated throughout their life cycle. The objective of pharmacovigilance systems is to monitor the safety of medicines after their commercialization; pharmacoepidemiological studies try to evaluate, in a systematic way, the beneficial and adverse effects of drugs when they are used outside the controlled environment of clinical trials; and economic evaluation aims to analyze the social profitability of drugs, that is, their efficiency, in order to help in decisions on price, financing and use.

In the following sections, the foundations of these three activities will be analyzed, taking a brief historical tour of their evolution in Spain, outlining the main challenges they face in the future.

2. Pharmacovigilance activities in Spain

2.1. Evolution of the Spanish Pharmacovigilance System

The activity of pharmacovigilance officially began in Spain in 1973 when the Spanish Ministry of Health published an order establishing the reporting of suspected adverse drug reactions (ADRs) to the National Centre of Pharmacobiology as an obligation for physicians and pharmaceutical laboratories [3]. However, it was not until 1982 when the Clinical Pharmacology Division of the Autonomous University of Barcelona (UAB) was granted a research project aimed at starting a pilot program of voluntary reporting of ADRs in Catalonia. In October 1982, all the Catalan medical doctors received a triptych with information on the pharmacovigilance program along with a "yellow card" to notify ADRs. The first suspected ADR was reported in September 1982 [3].

In 1984, the Spanish Ministry of Health, with the expert's advice of the WHO European Regional Office, agreed to set up the Spanish Pharmacovigilance System for medicines of human use (SPhVS) following a decentralized model according to the new political structure of Spain, being the Clinical Pharmacology Division of the UAB selected as the coordinator. After a pilot phase with 3 regional centers, the pharmacovigilance program spread to all the other autonomous communities. In 1992, the Pharmacology Department of the National Center of Pharmacobiology (Institute of Health Carlos III) was designated as the SPhVS coordinator [3]. In 1999 this department was integrated in the Division of Pharmacoepidemiology and Pharmacovigilance in the newly created Spanish Agency of Medicines and Medical Devices (AEMPS).

Currently, the SPhVS is made up of seventeenth pharmacovigilance regional centers. All the suspected ADRs reported to each one of the seventeenth regional Pharmacovigilance centers are included in the National pharmacovigilance database (FEDRA, Spanish Pharmacovigilance Data on ADRs). In addition, all suspected signals are included in the agenda of the Technical Committee of the Spanish Pharmacovigilance System and are discussed during its meetings. At the same time, the Technical Committee coordinates its activities and decisions with those of the Pharmacovigilance Risk assessment Committee (PRAC) of the European Medicines Agency (EMA).

2.2. Consolidation and achievements of the Spanish Pharmacovigilance System

Pharmacovigilance is a public health activity that covers all the activities aimed at the identification, characterization, quantification, and evaluation of risks associated with the use of medicines, as well as the implementation of the necessary measures for maintaining a favorable benefit–risk, and the evaluation of their impact.

Clinical pharmacologists have been a key group in the implementation and consolidation of pharmacovigilance in Spain and continue to be closely linked to this activity. They are present in the Spanish Medicines Agency, in regional pharmacovigilance centers, in specific programs in hospitals and primary care centers, in pharmaceutical companies and in the field of research.

Since the early stages of the program, spontaneous reporting has been considered a cornerstone method for signal detection and risk identification. In many cases, reported spontaneous ADRs have allowed the identification of signals about safety problems with medicines, which have finally led to regulatory measures. These measures have caused changes in the product information, changes to the scope of prescription, or in cases of unfavorable benefit-risk ratio, the withdrawal of the marketing authorization. In all these decisions, the activity of the SPhVS has been crucial [4].

During the first decades of operation, some identified ADRs allowed the withdrawal of drugs with scarce therapeutic value [5]. Since the creation of the European Medicines Agency in 1995, Spain has been part of the network of regulatory agencies of the member states that carry out the signal generation and evaluation process in a coordinated manner [4]. Table 1 shows some examples of drugs withdrawn in Spain for safety reasons or that motivated other types of regulatory measures in which the SPhVS has participated in. For signal detection, the pharmacovigilance centers carry out a qualitative evaluation of the reports on a case by case basis. In addition, the signal detection process is supported by a disproportionality analysis that computes the reporting odds ratio and the information component as measures of disproportionality. Since 2017, with the aim of optimizing the use of the data collected for signal generation, FEDRA (version 3.0) has incorporated automatic tools for this quantitative analysis.

Many published analyzes of case series collected through spontaneous reporting in Spain have made it possible to identify or characterize adverse drug reactions [5-9].

In 2023, FEDRA gathered about 550,000 reports. A total of 60,261 reports of suspected ADRs were received in 2022. 69.4% of them were reported directly to the SPhVS and the rest were reported on mainly through the pharmaceutical industry. Out of cases reported on directly to the SPhVS, 67% were carried out by health professionals, mainly primary care physicians and, 33% by citizens. The reporting rate in 2022 was at 88 cases per 100,000 inhabitants (www.aemps.gob.es/vigilancia/medicamentosUsoHumano/SEFV-H/docs/Informe_Anual_FV-2022.pdf).

In order to facilitate the reporting of ADRs and to increase the reporting rate, a national web-based reporting form has been implemented (www.notificaRAM.es).

Patients have played an active role in drug safety monitoring and their contribution has proven to be useful. The SPhVS incorporated direct patient reporting in 2013. Throughout these 10 years, out of the 211,875 spontaneous ADR reports sent directly to the regional pharmacovigilance centers, 36% were reported by citizens. Their participation has progressively increased since 2013, from 127 in the first year of its implementation to around 1000 in 2020. The social relevance that pharmacovigilance acquired with the monitoring of pandemic vaccines against COVID-19 dramatically increased citizen participation. In 2021, 15,500 reports from citizens were received.

Table 1
Signals identified and regulatory measures adopted.

Drug	Adverse reaction and regulatory measure	Year
Cinepacide	Agranulocytosis. Withdrawal.	1987
Citiolone	Dysgeusia. Product information changes.	1987
Cinnaricin, flunaricin	Parkinsonism and depression. Product information changes.	1989
Bendazac	Hepatotoxicity. Withdrawal.	1992
Glafenin	Hypersensitivity and hepatotoxicity. Withdrawal.	1992
Gangliosides	Guillain-Barre syndrome. Withdrawal.	1993
Droxicam	Hepatotoxicity. Withdrawal.	1994
Pyrityldione	Agranulocytosis. Withdrawal.	1996
Ebrotidine	Hepatotoxicity. Withdrawal.	1998
Dinoprostone	Disseminated intravascular coagulation. Product information changes.	2000
Cerivastatin	Rhabdomyolysis. Withdrawal.	2001
Nimesulide	Hepatotoxicity. Withdrawal.	2002
Dobesilate	Agranulocytosis. Product information changes.	2002
Tetrabamate	Hepatotoxicity. Withdrawal.	2002
Infliximab	Tuberculosis infection. Product information changes.	2002
Nefazodone	Hepatotoxicity. Withdrawal.	2003
Veralipride	Extrapyramidal and psychiatric reactions. Withdrawal.	2005
Carisoprodol	Abuse and dependency. Product information changes.	2005
Rimonabant	Psychiatric reactions. Withdrawal.	2008
Leuprorelin-containing depot medicinal products	Medication errors. Product information changes	2014
Paritaprevir-ombitasvir-ritonavir	Depression and suicidal ideation. Product information changes.	2017
Ingenol mebutate	Skin cancer. Withdrawal.	2020
Anti-tumour necrosis factor (TNF) drugs	Kaposi's sarcoma. Product information changes.	2020
Tramadol	Hiccup. Product information changes.	2021
Hydroxicloroquine	Psychosis and psychotic disorders. Suicide. Product information changes.	2021
Vortioxetine	Hyponatremia. Product information changes.	2021
Labetalol	Raynaud phenomena. Product information changes.	2021

To prevent ADRs, it is important to inform healthcare professionals as well as the general population about them. Risk management and communication activities play a central role in the pharmacovigilance system, -modifying the terms of marketing authorization when necessary and elaborating safety announcements- and several strategies are used for disseminating safety information. Moreover, in the last few years, progress has also been made in transparency, making public information available on reported adverse reactions on the AEMPS website.

A relevant task that has begun to be addressed in recent years is monitoring the effectiveness of the risk minimization measures adopted. Although some steps have been taken, further developments are still necessary in this area.

2.3. Development of the spontaneous ADR reporting program in health care centers and other pharmacovigilance activities

Despite the recognized value of the spontaneous ADR reporting program in the identification of unexpected and unknown ADRs, one of its most important limitations is the underreporting of ADRs. In Spain, the most recent Pharmacovigilance Royal Decree (in 2013) still recognizes the reporting of ADRs and collaboration with the SPhVS as an obligation for health care professionals (HCPs) [10]. In spite of this, the rate of ADR reporting is no higher than that described previously (less than 10% of ADRs) [11].

In order to increase the rate of ADR reporting and to promote pharmacovigilance activities in hospitals, several initiatives led by clinical pharmacologists have been described. For example, a multifaceted intervention based on periodic educational meetings and economic incentives to the physicians in the context of healthcare management agreements in a hospital was associated with an increase in the median number of reported ADRs per year, their severity and in the number of reported unknown ADRs in comparison to a similar period before the intervention [12]. In addition, other pharmacovigilance strategies carried out in order to complement the spontaneous ADR reporting program in hospitals are being developed. For instance, a systematic review of all admitted cases with at least one diagnosis of a selected list of assessed diagnoses or systematic review of all admitted cases with at least a laboratory test anomaly of a selected laboratory list of trigger anomalies is being performed [13,14]. In addition, pharmacogenetics is being progressively implemented in clinical practice and has recently become another important tool to not only assess the role of genetic variations in the toxicity of drugs but also to better characterize some ADRs in order to make recommendations to prevent their occurrence [15,16].

There are also some published experiences where interest has been focused on the follow-up of patients treated with a specific group of drugs and the description of their ADR profile in real world practice. Amaro-Hosey et al. in a prospective study have recently described the incidence and most frequent ADRs in pediatric patients with cancer treated with one or more drugs from a previous agreed list of drugs used to treat cancer or its complications [17]. In another prospective study, Sabaté et al. described the incidence of all ADRs and especially that of immune mediated ADRs in a cohort of adult patients with cancer exposed to anti-PD1 or anti-PDL1 in monotherapy [18]. In addition, Montané et al. analysed the incidence and the risk factors of drug-related deaths in a cohort of hospital inpatients with a death diagnosed from a list of predefined medical conditions potentially caused by drugs [19].

The monitoring of ADRs through post-marketing pharmacovigilance systems is vital for patient safety, since unknown or unexpected ADRs often appear during routine clinical practice, when a larger number of people are exposed to drug use. Although the spontaneous ADR reporting program is hampered by the low rate of reporting, it is one of the most used post-marketing drug surveillance systems. In Spain, the spontaneous ADR reporting program has come a long way and, is now fully consolidated. However, it is in continuous evaluation and development with the aim of adapting it to new scenarios and exploring new tools such as mobile technology and social media to identify data of potential new risks. For a safe pharmacotherapeutic practice in patient care, awareness of ADRs is important and for this reason, healthcare professionals need to acquire pharmacovigilance competencies. For a better pharmacovigilance, understanding the importance of pharmacovigilance, preventing, recognizing and reporting ADRs are key factors, and this should be incorporated into the educational programs of healthcare professionals.

In addition, several other pharmacovigilance strategies are being carried out especially in some hospitals in order to complement the spontaneous ADR reporting program (for example, a systematic review of admitted patients guided by a selected list of assessed diagnosis or by a selected list of laboratory triggers or pharmacogenetic assessments). The hospital setting brings us the opportunity not only to identify serious and unknown ADRs but also to document them with high quality information and then offer all this information to the pharmacovigilance system. However, an extra effort still must be made in order to facilitate the systematic and electronic registration and exploitation of all ADR information in a hospital network.

3. Pharmacoepidemiology

Pharmacoepidemiology is the science that applies epidemiologic reasoning, methods and knowledge to the study of the uses and effects (beneficial or adverse) of drugs in human populations [20], in real-life conditions. This discipline has been the result of the successful

merging of clinical pharmacology, which provides the scope (the study of drugs in human beings), and epidemiology, which provides the method to measure such uses and effects. In operative terms, pharmacoepidemiology can be divided in two main areas: 1) Drug utilization studies, aimed to examine both quantitative and qualitative aspects of the use of drugs and identify its determinants; and 2) the conduct of epidemiological studies to assess the causal relationship between drugs and events, to measure its population impact, and to identify the potential effect modifiers (e.g. predisposing or preventive factors of drug-event associations). Increasingly, pharmacoepidemiology is also an important tool to evaluate the effectiveness of risk minimization measures [21]. Pharmacoepidemiology had its main application in pharmacovigilance but over time has been progressively used to assess the effectiveness of drugs in real-life conditions (in particular, comparative effectiveness). It is a historical fact, yet not widely known, that the cardioprotective effect of aspirin was first identified in a pharmacoepidemiological study well before the completion of randomized clinical trials [22].

3.1. An outline of the history of the Spanish pharmacoepidemiology

Two are the main historical roots of pharmacoepidemiology. One is the drug utilization studies that started in Europe over the sixties aimed to compare drug consumption in different countries, which ended up with the creation of the Drug Utilization Research Group and the DDD methodology [23]. The other, and doubtless the most important one, was pharmacovigilance and the efforts made to develop methods to complement the spontaneous reporting schemes during the late sixties and early seventies. In this context, it deserves to mention: 1) the Boston Collaborative Drug Surveillance Program (BCDSP), initially conceived as an intensive monitoring program to assess the drug-related events during hospitalization, and that progressively evolved to analyze the risk of hospitalization associated with outpatient drug use [24]; 2) the application of the case-control methodology for drug safety evaluation [25,26] and 3) the setting-up of the Prescription Event Monitoring in the UK [27], as an approach to rapidly build cohorts of users and followed them up to estimate the incidence of new drug events not detected during clinical development. But the most important step in the historical evolution of pharmacoepidemiology was taken in 1978, when the BCDSP made an agreement with the Group Health Co-operative of Puget Sound, a health maintenance organization (HMO) in Seattle, in order to explore the possibilities of performing pharmacoepidemiological studies using the administrative database from this HMO [24]. As a result, a study was carried out examining the effects of postmenopausal estrogen use and the risk of endometrial cancer [28], being the first paper of pharmacoepidemiological research in history using a computerized database.

Another important step was taken in 1988, when the GPRD (General Practice Research Database, now called CPRD, Clinical Practice Research Datalink), the first integral database created for research purposes, came into play in the UK [29]. Shortly, the GPRD became the reference for many others which would come afterwards [30].

The word “pharmacoepidemiology” appeared for the first time in a paper by D. Lawson in the British Medical Journal in 1985. In such year it was held in Minneapolis an international conference to discuss the uses for Medicaid databases in pharmacoepidemiology, that was the embryo of the International Society of Pharmacoepidemiology (ISPE). A few years later, pharmacoepidemiology came of age when two reference books were published [31,32].

In Spain, the first stone of pharmacoepidemiology was settled down in the early eighties by JR Laporte and his colleagues at the UAB and Hospital Vall dHebron. They strongly contributed to the creation of the SPhvS-H (see previous section), performed important case-control studies [33], took part in the International Agranulocytosis and Aplastic Anemia Study (1986) [34] and, last but not least, published the book “Principios de Epidemiología del Medicamento” (Principles of Drug Epidemiology) in 1983 [35]. This book became the reference for many Spanish-speaking clinical pharmacologists interested in pharmacoepidemiology on both sides of the Atlantic. Of note, it preceded in several years the books considered the worldwide references for the discipline.

Another cornerstone in the Spanish pharmacoepidemiology was the creation of CEIFE (Centro Español de Investigación Farmacoepidemiológica) in 1994 by L. A. García Rodríguez, the most renowned and cited Spanish pharmacoepidemiologist. After being trained in epidemiological methods at Harvard and having important positions at the pharmaceutical industry in the late eighties, LA García-Rodríguez started to work at the BCDSP in 1990, where he helped to test new automated databases for pharmacoepidemiologic research such as the Canadian Saskatchewan [36], and carried out the first studies using the GPRD [37]. Since the creation of CEIFE he continued to work with the UK databases (GPRD-CPRD and THIN, the Health Improvement Network), and provided the know-how to build up BIFAP in Spain, among other contributions worldwide (http://www.ceife.es).

It is also worth to mention the contribution of the pharmacoepidemiological team at the National Centre of Pharmacobiology, integrated in the AEMPS in 1999 with the significative name of “Division of Pharmacoepidemiology and Pharmacovigilance” (DPP). This group performed over the nineties numerous drug utilization studies using the consumption data of the General Directorate of Pharmacy which ended up in the Observatory for Drug Use, now publicly available at the AEMPs website as an interactive tool (https://www.aemps.gob.es/medicamentos-de-uso-humano/observatorio-de-uso-de-medicamentos).
Since 1998, the DPP started a collaboration with CEIFE to conduct epidemiological studies to assess drug-events associations using the GPRD [38,39] and in 2000 both groups made an alliance to run the pilot phase of BIFAP, the first database available in Spain [40], officially adopted by the AEMPS in 2003 (see next section).

The development of pharmacoepidemiology in Spain run parallel to the development of the Spanish Pharmacovigilance System and their regional centers were important actors in its evolution. Some of them, set up specific centers for pharmacoepidemiology research, such as the Institute of Pharmacoepidemiology at the University of Valladolid, created in 1999 (now called CESME, “Centro de Estudios sobre la Seguridad de los medicamentos”) (http://albergueweb1.uva.es/cesme/).

Other Spanish pharmacoepidemiologists have had important contributions to the field. Among them, it is worth highlighting S. Pérez-Gutthann, leader of diverse pharmacoepidemiological research groups in the private sector and S. Hernández-Díaz, professor of epidemiology and director of the pharmacoepidemiology program at Harvard T.H. Chan School of Public Health. Both were presidents of the ISPE in 2004 and 2016, respectively.

As early as 2006, the top-range law that regulates medicines and medical devices in Spain (Ley de Garantías y Uso Racional de los medicamentos), included an article entitled “Pharmacoepidemiology and risk management” which was an important milestone, placing pharmacoepidemiology at the very center of the safety evaluation of drugs in a regulatory framework.

3.2. The emergence of automated databases: a shift in the paradigm

The evolution of pharmacoepidemiology has been strongly linked to the availability of automated data sources that contain healthcare data obtained from routine clinical practice. Thus, available data sources reflect the characteristics of the respective healthcare systems and organizations. Broadly speaking, they capture the data from the encounters of patients with the health care system. In this context, two main types of databases can be mentioned: 1) Those based in electronic healthcare records (EHR) which contain information directly collected by healthcare professionals to support patients care and secondarily used for research purposes; and 2) claims databases that are primarily built for administrative purposes (e.g. management of payments and

reimbursement) of healthcare organizations and secondarily used for research.

In order to ideally gather all the information required to implement a research protocol, real world data should bring together different levels of care to cover as much as possible all the interactions of the patient with the healthcare system and other relevant information (i.e. social, educative, demographic). This is the purpose of what are called integral databases. Other scheme consists of connecting different "data banks" such as hospital discharge records, primary care medical records, pharmacy dispensation records, healthcare registration data and others through unique patient identifiers (record-linkage databases).

The range of characteristics relevant for characterizing a database that should be considered to gauge its appropriateness for a specific study is more extensive that the concepts mentioned above. For this purpose, catalogues of metadata are being defined to identify databases that can potentially serve as data source in pharmacoepidemiology for specific research questions (31 May 2022 EMA/563896/2022 List of metadata for Real World Data catalogues).

In Spain, almost all healthcare and administrative records are nowadays electronically captured and stored in databases. Nonetheless, the number of multipurpose, population-based databases used for pharmacoepidemiological research is much more limited. To achieve this, the managing organization needs to maintain a dedicated team with the capacity to extract, curate, normalize and analyze the data to execute a research protocol. Table 2 summarizes currently active data sources and institutions in Spain with contrasted experience in pharmacoepidemiological research [41-43]. These data sources have developed their own procedures and governance to make data available to researchers [44-46]. The one of BIFAP, by far the oldest and largest database in Spain, is shown in Fig. 2.

Although pharmacoepidemiological studies conducted in population-based databases often contain information on millions of patients, they can still be underpowered if outcomes or exposure of interest are rare, or the interest is focused on specific subgroups. Also, the pattern of drug utilization may differ across regions and the study of these different patterns may have interest per se, or it may have a differential impact on the safety and effectiveness of drugs. For these reasons, it is growing the need to perform multi-database studies, that is, studies in which at least two healthcare databases, not linked with each other at individual level, are used. The simplest strategy to perform multi-database studies is by sharing a common research protocol with analysis of data remaining local. However, the most efficient way to proceed is to perform a single central analysis of data and have all data sources fully adapted ("translated") to a Common Data Model. In this scheme, patient-level data remain local and the studies are performed in what is called a federated network [47].

A different type of real-world data source, designed for specific purposes, is the patient registries. These are organized systems that collect uniform data from a population defined by a particular disease, condition or exposure. In Spain there are several examples of exposure registries (e.g. BIOBADASER and BIOBADADERM, devoted to the surveillance of biological drugs used in the treatment of rheumatologic and dermatologic diseases, respectively) and also several examples of disease registries (such as PIELenRed for serious cutaneous adverse reactions coordinated by the University of Alcalá, and the Spanish DILI Registry coordinated by the University of Málaga).

3.3. The future of pharmacoepidemiology

In the coming years, we will see a growing use of EHRs for pharmacoepidemiologic research and an increase in their interoperability [48,49]. To that end, the European Union has launched the DARWIN EU Project (https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu), in which the OMOP common data model has been selected in order to ensure full interoperability of the data with respect to structure (syntactic interoperability) and coding systems (semantic interoperability) (https://www.ohdsi.org/data-standardization/). Furthermore, an initiative to promote better exchange and access to different types of health data in the European Union has been proposed by the European Commission, including a regulation to set up the European Health Data Space. This is a health-specific data sharing framework establishing clear rules, common standards and practices, infrastructures, and an overarching governance guideline for the use of electronic health data by patients and for research, innovation, policy making, patient safety, statistics or regulatory purposes.

Pharmacoepidemiology will progressively adopt new methods for causal inference [50], that will be a qualitative step forward in the

Table 2
Databases available in Spain: Main features*.

Data source (institution)	Geographical coverage and no. of active subjects	First data collection and update frequency	Type of data	References and websites
BIFAP (AEMPS)	Nine Autonomous Communities 21 million	From 2001, updated at least every 6 months	Primary care EHRs. Hospital discharge data (CMBD). Pharmacy (community)	Maciá-Martínez et al. [45] http://www.bifap.org/
SIDIAP (IDIAP)	Catalonia 5.8 million	From 2005, updated every 6 months	Primary care EHRs. Hospital discharge data (CMBD). Pharmacy (community)	Recalde Met al., [46] https://www.sidiap.org/index.php/en/
VID (FISABIO)	Valencia Region. 5 million	From 2008, updated at least every 6 months	Primary and specialist care EHRs. Hospital discharge data (CMBD). Pharmacy (community and hospital)	García-Sempere A et al., [44] https://www.san.gva.es/es/web/investigacio/solicitud-datos-sia-gaia

BIFAP: Pharmacoepidemiological Research Database in Public Health Systems
AEMPS: Spanish Agency of Medicines and Medical Devices
SIDIAP: The Information System for Research in Primary Care
IDIAP: Institute of Research in Primary Care Jordi Gol (IDIAP Jordi Gol)
VID: Valencia Health System Integrated Database
FISABIO: Valencia Foundation for the Promotion of Health and Biomedical Research)
*For a list of publications carried out with these databases, the reader may access to their respective webpages: http://www.bifap.org/, for publications using BIFAP; https://www.sidiap.org/index.php/es/activitat-4 for publications using SIDIAP.

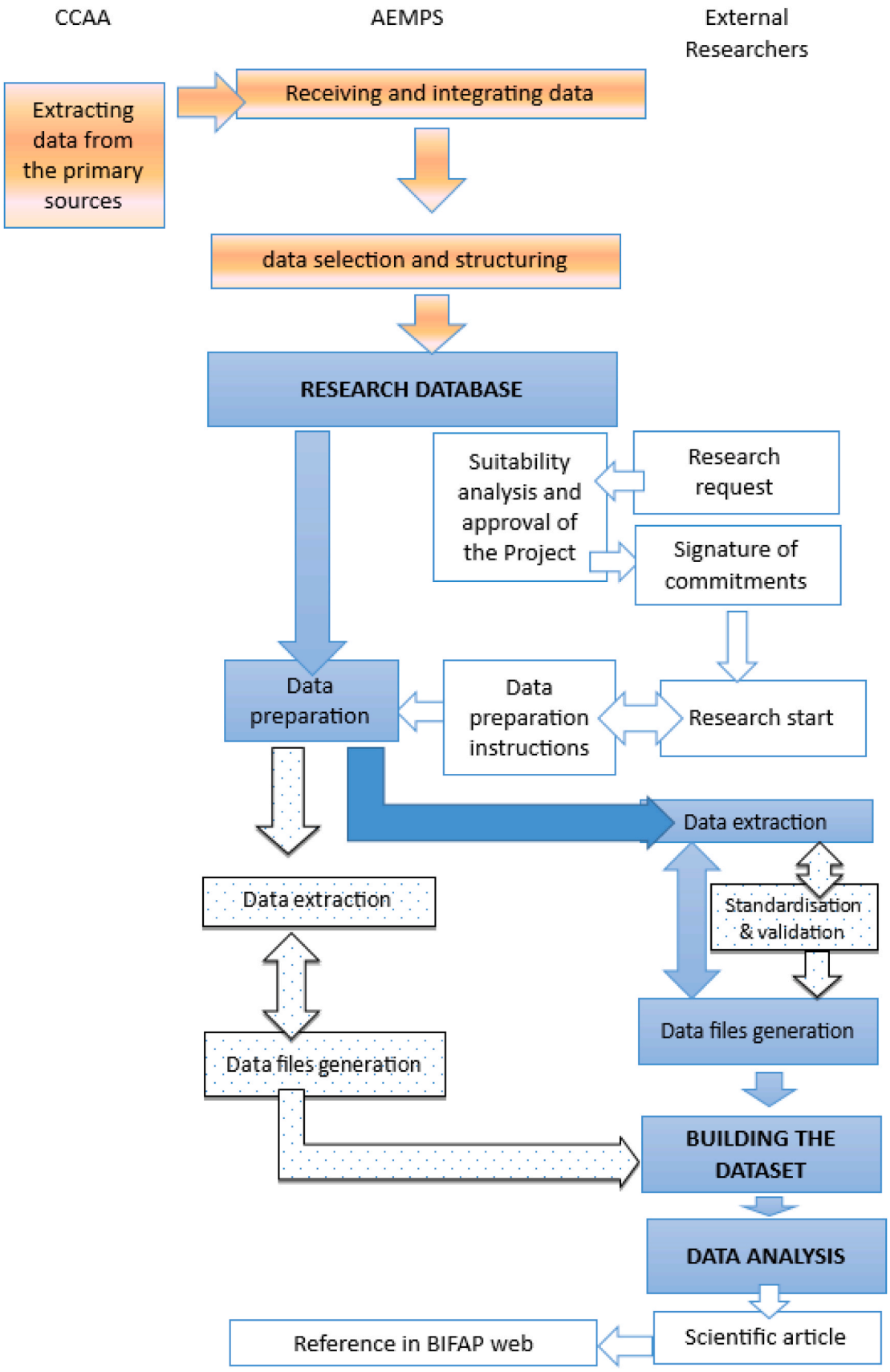

Fig. 2. Flow of data processing operations (data processing and data transfer) to perform BIFAP studies by external researchers.

design, conception, analysis and interpretation of data.

Finally, we expect an increasing connection between pharmacoepidemiologic and pharmacogenomic data. Disease registries offer an ideal scenario for that purpose [51].

4. Economic evaluation of drugs

As Professor Allan Williams, one of the precursors of health economics, pointed out more than three decades ago, economics can be applied to issues that at first glance do not seem economic, such as identifying which is the best treatment that a national system of health should provide to a patient with a specific disease. The existence of limited resources, together with a health demand that tends to be infinite and the continuous introduction of new, more effective, but also more expensive technologies, has contributed to incorporate the analysis of the economic impact of the use of drugs into the evaluation process of new medicines.

Schematically, there are two different strategies to control the increase in pharmaceutical spending. The first is a cost-focused strategy. In it, most of the new medicines are financed, but to be able to face the high cost it is necessary to implement control measures that reduce the budgetary impact, such as the reduction of prices, the introduction of copayments, auctions, and centralized purchases, among others. The second is a value-based strategy, where not all innovations are financed, and their payment is linked to the value they bring to the system [52]. This last strategy, characteristic of countries with more advanced healthcare systems, requires a clear definition of what is meant by value.

Although different methods have been proposed to assess the value of a drug, cost-effectiveness analysis is currently considered the reference method, since it has a solid conceptual basis [53,54] and is also supported by its successful use in a growing number of countries. The economic evaluation of health interventions has been defined as “the comparative analysis of different health interventions in terms of costs and health outcomes” [55]. Such evaluation can be applied to any type of intervention or health program, but in practice, the vast majority of economic evaluations focus on medicines. Cost effectiveness evaluation has been called the “fourth barrier” and, in practice, involves a double evaluation. On the one hand, the evaluation of efficacy, safety and quality continues to be the basis for marketing authorization by regulatory agencies. Subsequently, the evaluation of efficiency, based on the cost-effectiveness analysis, is used to decide on the price, financing and the place of the drug in therapy.

In the early 1990s, Australia and Canada were the first countries to apply the criterion of efficiency to public reimbursement for medicines’ decisions. With different peculiarities, this model was adopted by a growing number of countries, highlighting the case of the United Kingdom, where the creation of NICE (National Institute for Care and Health Excellence) in 1999 became a reference in terms of systematic implementation of the cost-effectiveness criterion in the selection of new drugs. Sweden, the Netherlands, Portugal, or France, in Europe, or South Korea and Japan, in Asia were some of the countries that also incorporated the cost-effectiveness criterion into their decisions [56,57].

More than thirty years ago, Spain was one of the first countries to develop methodological guidelines for carrying out economic evaluations of health interventions [58]. Despite this, in practice, the use of the efficiency criterion in decisions on the price and financing of new drugs has been marginal. Interestingly, this last fact is not due to the lack of specific legislation on the subject. The Medicines Law of 1990 already introduced the idea of selective and not indiscriminate financing, linked to the concept of efficiency; and the Royal Decree Law 9/2011 on measures to improve the quality and cohesion of the National Health System (RDL 9/2011) established that, for the inclusion of new drugs in public financing, "the value of therapeutic and social benefit of the medication and its incremental clinical benefit taking into account its cost-effectiveness relationship”. We also have a Network of Health Technology Assessment Agencies, although its assessment activity has focused mainly on non-pharmacological technologies. And the number of cost-effectiveness studies published by Spanish authors has grown steadily in recent years. Therefore, it seems that the barriers to the implementation of the economic evaluation of medicines in Spain have more to do with cultural and political factors, such as the fear of losing control over pricing and financing decisions, the reluctance to said decisions are transparent, or the existence of conflicts of powers between the central and regional administrations [59]. The application of the efficiency criterion aims to contribute to improving the consistency, transparency and predictability of decisions, characteristics that, unfortunately, are not among the strengths of our healthcare system [60].

There are some indications that the situation described could be changing. In 2019, at the proposal of the Ministry of Health, the Advisory Committee for the Financing of the Pharmaceutical Benefit of the National Health System was created, to provide advice on the economic evaluation necessary to support the decisions of the Inter-ministerial Commission on Prices of Medicines. In addition, in 2013, the Pharmacy Commission of the Interterritorial Health Council approved the implementation of Therapeutic Positioning Reports (IPTs), coordinated by the Spanish Agency for Medicines and with participation of the General Directorate of Pharmacy and the Autonomous Communities [59]. The objective of the IPTs was to conduct a complete clinical evaluation of the new medicines to position them in relation to existing medicines. Such evaluation required the systematic incorporation of its comparative effectiveness and its efficiency. However, in practice, in the first seven years of the life of the IPTs, economic information has not been incorporated into the documents, even though 44% of the IPTs indicated in their conclusion that efficiency should be a fundamental element in the selection of the new drug [61]. In 2020, a new Plan was launched to consolidate the IPTs of medicines in the National Health System. In this new stage, the deficiencies were intended to be corrected and some of the new IPTs began to incorporate an economic evaluation, although the procedure for preparing the evaluations, their anchoring in the financing process or the methodology used still need to be defined exactly.

The situation described in the previous paragraphs reflects the challenges that lie ahead to ensure that the economic evaluation of medicines is successfully implemented in Spain. The main barrier has been the lack of political will, since the other barriers can be overcome relatively easily. We are facing the difficult challenge of implementing modern prioritization methods, based on predictability, consistency, and transparency, within an evaluation culture still anchored in the past. The paradigm shift necessarily involves well defining the criteria that constitute the value of a drug [62], clearly separating the evaluation of the level of innovation (efficacy, safety, comparative effectiveness) from its efficiency (cost-effectiveness), avoiding the unfortunate “reverse evaluations” that question the degree of innovation of drugs that have a high budgetary impact. It is also necessary to promote a culture of evaluation, in which clinical and economic re-evaluation is systematically conducted when new information becomes available on the effects and costs of drugs in the conditions of usual clinical practice. And, above all, it is necessary to assume the idea that the more limited the health resources are, the more necessary it is to invest in evaluation.

Clinical pharmacology is a medical specialty that is especially suitable for coping with the task of evaluating the efficiency of medicines. Pharmacoeconomic analyses require a thorough knowledge of clinical research methodology, which is the essence of the training of a specialist in clinical pharmacology. In addition, one of the greatest advantages of the specialty when it comes to the comprehensive evaluation of a drug is the absence of conflicts of interest. The clinical pharmacology services are not responsible for the budgetary management of medicines, which facilitates the independence of their evaluations.

5. Conclusion

Clinical pharmacology has classically focused on the clinical

research activities conducted before new drugs' commercialization (p.e. the evaluation of the efficacy and safety through phase I-III clinical trials). But nowadays regulatory approval cannot be considered the last step in the evaluation of new medicines but as a continuous process that necessarily must last through the whole life cycle of the drug, including how medicines work in the real-life setting.

The increasing number of conditional drug approvals subject to additional post marketing assessment; the growing evidence that the beneficial and adverse effects of a drug under the ideal conditions of use that take place during the clinical trial are different from its effectiveness and safety when used in the real world; or the need to evaluate the economic impact of new drugs once they are incorporated into the therapeutic arsenal, makes it essential that Clinical pharmacology expand its field of action and become an essential medical specialty that helps the National Health System to decide which drugs can be offered to the population and how they should be used, taking into account their effects and associated costs. Clinical pharmacology should not miss the opportunity to rediscover its main objective, which is to achieve a more rational use of medicines, considering all the available evidence throughout their entire life cycle.

Authors statement

The work has not been published previously, it is not under consideration for publication elsewhere, and it has been reviewed and approved by all authors. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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