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SPECIAL ISSUE

SYMPOSIUM ON INNOVATION IN PHARMACOVIGILANCE

From the Director

The **Portuguese National Pharmacovigilance System (SNF)** was created in 1992 and more than 25 years on is now a mature, robust and efficient system coordinated by Infarmed and involving regional pharmacovigilance units, marketing authorization holders, healthcare professionals and organizations, patients and the European Medicines Agency (EMA). Since its inception the SNF has gone through various stages with an impact on its staff's competencies, on its procedures and on its safety information technology support.

Decision making processes concerning medicinal product safety have evolved significantly, with increasing harmonization and transparency. In addition to healthcare professionals, those processes now involve patients, who have become able since 2012 to autonomously and directly report adverse drug reactions (ADRs) to authorities.

The "**new pharmacovigilance**" is about more and better access of the public to information, reinforced communication and greater cooperation among member states in work sharing with reduced duplication of efforts. Portugal has met the challenges, incorporated every breakthrough and gained a significant position within the Pharmacovigilance Risk Assessment Committee (PRAC).

In 2017, the SNF underwent its most recent restructuring period aiming to increase the system's **proactivity and proximity** to healthcare professionals and patients: new pharmacovigilance units were set up and a new **ADR Portal** launched. ADR reporting has become easier, faster and more accessible, and matches the new features of the European database EudraVigilance, with ensured interoperability and information exchange.

This reorganization has been very positive and is reflected in a significant increase in the number of ADR cases received. This helps to deepen the knowledge of the safety profile of medicinal products and to implement risk minimization measures for the protection of the public's health.

To mark the SNF's 25th anniversary and its achievements, an ***Innovation in Pharmacovigilance* symposium** took place on 10th December 2018 and an up-to-date manual for professionals and academicians (***Pharmacovigilance in Portugal: 25 years***) was launched.

INDEX CARD

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Innovation in Pharmacovigilance Symposium

This symposium took place on 10th December 2018 at INFARMED and included four topical sessions (papers presented available **here**).

The Chair of the Board of Directors, Maria do Céu Machado, opened the event. The scientific programme was preceded by a special session for the launching of the book ***Pharmacovigilance in Portugal: 25 years***, an INFARMED publication coordinated by the Board Member Sofia Oliveira Martins and by the Medicines Risk Management Department.

"This book is to be a reference for pre and postgraduate teaching, as well as for study and research by healthcare professionals and organizations, universities, and other institutions."

(*in* Preface and Notes from the Editor, Sofia Oliveira Martins and Maria do Céu Machado)

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E-book **available soon at the Infarmed website.**

Session I

New methodologies in Pharmacovigilance: organization and implementation

Moderator:
Ana Paula Martins, Chair of the Portuguese Pharmacists' Council.

Speakers:
Dolores Montero, from the Spanish Medicines Agency – AEMPS;
Astrid Moura Vicente, from Instituto Nacional de Saúde Dr. Ricardo Jorge;
Francisco Batel Marques, from Coimbra University Faculty of Pharmacy and AIBILI;
Carla Torre, from Lisbon University Faculty of Pharmacy.

BIFAP. Dolores Montero presented the *Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria* (BIFAP), an electronic longitudinal population record extracted from the Spanish primary care physicians' regional information systems. This collaborative project involves 5,862 doctors and data from 9.4 million patients (approximately 20% of the Spanish population). It does not include any personal identification items, rather patient health status details and their medicinal product use patterns (in Spain about 80% of medicines are prescribed in the primary care setting). The main reason why BIFAP was created was to facilitate pharmacoepidemiological research, and five papers have already been published in international journals which were based on analyses of the data contained in the electronic platform.

Pharmacogenomics as applied to pharmacovigilance. Astrid Moura Vicente gave an updated summary of current applied pharmacogenomics with an emphasis on the **CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines and the RAM-Predict** project. The latter has been developed by the Portuguese INSA public health institute in collaboration with Infarmed and aims to define predictive adverse drug reaction models, including genetic susceptibility, clinical data and other factors, which can be directly applied in clinical practice.

Collaborative pharmacovigilance networks. These were discussed by Francisco Batel Marques based on his experience with **DruSER.Net (Drug Safety and Effectiveness Research Network**), which was created and developed by the Coimbra Regional Pharmacovigilance Unit in cooperation with local hospitals and health centres. Its main goal is to promote post-marketing medicines safety and effectiveness monitoring and research, and thus to help to capture real world data and minimize iatrogenic risk. DruSER.Net has several **ongoing projects**, such as: a collaboration with the Coimbra University Hospital's Immunology and Allergy Department to identify and report drug hypersensitivity reactions; a retrospective analysis at network health centre level to identify direct oral anticoagulant-associated haemorrhagic events; and the characterization, together with the Lower Vouga Hospital Centre, of a series of cases of enoxaparin-associated intraabdominal haemorrhage.

Identification of innovator drug adverse events through a community pharmacy based intensive monitoring methodology. A study from this project was presented by Carla Torre on the frequency, timeline and factors associated with adverse events with blood glucose lowering agents, including self-declared hypoglycaemic episodes. Given their geographical dissemination and proximity to patients, community pharmacies can play a relevant role by obaining **real life medicinal product use data**, namely when following up inception cohorts exposed to innovative medicines.

Session II

Technology at the service of Pharmacovigilance

Moderator:
Fátima Canedo, Head of Infarmed's Medicines Risk Management Department.

Speakers:
David Lewis, from Novartis;
Miguel Antunes, from Infarmed's Medicines Risk Management Department;
Inês Ribeiro Vaz, from the Porto Regional Pharmacovigilance Unit;
Edurne Lázaro, from the Spanish Medicines Agency – AEMPS.

Intelligent automation of pharmacovigilance systems. David Lewis summed up the latest and most relevant developments in automation technology to support pharmacovigilance systems. He highlighted, among others, **machine learning** and **artificial intelligence** as tools for automatic identification of suspected adverse drug reactions. He went on to present what he considers to be the main challenges to their use, namely issues to do with process validation and practical implementation difficulties. Various examples were given, including the use of case processing routines and of algorithms. The latter are currently being studied from **three** distinct but complementary **viewpoints**: association studies (e.g, to detect outliers in clinical trials and postmarketing studies), filters (e.g., to improve the focus of use safety analyses), and prioritization (e.g., hierarchization of safety issue analyses by regulators). In spite of all these technological breakthroughs, they are only decision support tools and do not replace final human validation. The **WEB-RADR** project was additionally presented. This is a medicines use safety information collection system for non-structured sources such as **social media**..

Novel technological approaches in pharmacovigilance. Miguel Antunes addressed potential **health gains** resulting from the use of new technology. Some practical examples given included Portuguese National Pharmacovigilance System (SNF) projects, such as the use of natural language processing (NLP) software to support MedDRA coding, or inter-pharmacovigilance unit validation of causality assessment algorithms. An SNF ambition is to **provide physicians with further prescription support** in the near future through selective and personalized patient data.

The use of bayesian networks in pharmacovigilance. Inês Ribeiro Vaz presented a Porto Regional Pharmacovigilance Unit project that consisted of the development and validation of a bayesian network supporting causality assessment of cases of suspected ADRs. The gold standard was global introspection but the bayesian network achieved **shorter causality assessment times** and within the pre-defined 30-day frame. The network behaved **best for higher probability degrees** (precision and sensitivity for "Probable" of over 87%).

Information systems supporting the Spanish Medicines Agency (AEMPS). Edurne Lázaro presented the FEDRA information system which has recently been developed to facilitate ADR reporting and to support the interconnectedness among the seventeen pharmacovigilance centres located in the various Autonomous Communities of Spain. First implemented at the end of 2017, the system has already achieved its goals: in 2018 and up to the date of the conference 35,934 cases (**62% more than in 2017**) had been recorded and eleven potential pharmacovigilance signals raised, that is twice as many as in the preceding year.

Session III

New methodologies in Pharmacovigilance: patient participation

Moderator:
Inês Alves, from EUPATI Portugal.

Speakers:
Florence van Hunsel, from the Dutch pharmacovigilance centre Lareb;
João Nabais, patient representative;
Pedro Inácio, from Helsinki University.

Relevance of patient participation for medicines safety surveillance. Florence van Hunsel showed how patient participation in the European pharmacovigilance system has evolved through time and underscored that not every country has implemented the 2012 pharmacovigilance regulation's dispositions. The Netherlands is the country with the highest number of directly patient-originated ADR reports per million inhabitants, actually currently more than those reported by healthcare professionals. When the content of healthcare professionals' reports is compared to that of **patients**', the former includes more objective information, whereas the latter contains **more subjective data**. Patients give more details concerning the appearance and the evolution of the ADR, its seriousness and causality. Healthcare professionals on the other hand, tend to cover aspects relating to the suspected medicine (including dose and pharmaceutical form), as well as to the suspected role of concomitant medication. Regarding the relevance of patient provided information for pharmacovigilance signal detection, a Dutch agency study looked at the data received between 2010 and 2015 and concluded that **26.3% of safety signals** raised had originated from data from patients.

Importance of patient participation in the Pharmacovigilance System. João Nabais stressed that no pharmacovigilance system can reach maturity without patient participation. Although sufficient evidence on the **relevance of patient participation** already exists in international scientific literature, patients are not yet fully integrated in the Portuguese National Pharmacovigilance System, unlike in some other EU countries – this needs to change soon.

ADR reports from patients: from quantity to quality. Pedro Inácio has recently undertaken a perceptions study which included semistructured interviews to twelve key elements of the European pharmacovigilance system. He concluded that only a **minority** of the respondents had a **negative attitude** towards the integration of ADR reports from patients. Most pointed to the **importance** of creating a **culture of greater knowledge** among patients and healthcare professionals in order to promote more consistent and well-informed contributions. Few respondents mentioned any implementation hurdles, except for the need for agencies and the industry to allocate more resources to ADR case report processing.

Session IV

Portugal in the European Pharmacovigilance System

Moderador:
Rui Ivo, Infarmed's Vice-President.

Speakers:
Peter Arlett, from the European Medicines Agency;
Ana Sofia Martins, from Infarmed's Medicines Risk Management Department and Portuguese representative at the PRAC;
Mário Miguel Rosa, from the Lisbon University Faculty of Medicine and from Infarmed's Medicines Assessment Committee;
Rui Pombal, from Infarmed's Medicines Assessment Committee and representing Infarmed's Medicines Risk Management Department.

Special Session

The Future of European Pharmacovigilance. Peter Arlett highlighted the European system's goals: access to data, guideline development and currency, access to innovative medicines, effectiveness of risk minimization measures, and strengthening of the involvement of both patients and healthcare professionals. Pros and cons were also discussed.

Portugal's participation at the PRAC (Pharmacovigilance Risk Assessment Committee). Ana Sofia Martins showed how Infarmed has always taken an active part in the European pharmacovigilance system and even more so in the last few years. Portugal has not only had the lead or a monitoring role in numerous procedures, but has also been involved in European working parties that give support to pharmacovigilance activities. Recognition of the quality of Infarmed's participation in the European system is evident and Portugal is currently **PRAC Rapporteur for 67 medicinal products** and **Co-Rapporteur for another 44**, mostly from four major fields – hepatitis C, HIV, central nervous system, and oncology.

Clinical assessment for the PRAC. In order to enhance understanding of Portugal's involvement with the European pharmacovigilance system, Mário Miguel Rosa gave a clinical perspective with **real life examples** of procedures discussed at the PRAC. He further underscored how important it is for **clinical experts to take into account** the condition at hand and the population for which the medicinal product is indicated, its efficacy and safety, the existence of any therapeutic alternatives (pharmacologic or otherwise), the scientific aspects from the benefit-risk analysis, any applicable guidelines and regulatory precedents, as well as measures to consider in terms of regulatory risk management.

Clinical perspective on safety signal detection within the European system. Rui Pombal presented the **Infarmed (Medicines Risk Management Department) model for safety signal assessment and management**. This has **six facets**: causality assessment; enhancement of the quality and usefulness of clinical data inserted in the national and European databases; systematic periodical assessment of serious (death or life-threatening) cases; ad-hoc analysis of case clusters raising potential safety issues; real-time clinical advisory for the multidisciplinary signal management team; periodical assessment of the European eRMR (electronic Reaction Monitoring Reports) safety files as part of an intensive work-sharing system within which Portugal is in charge of monitoring 38 substances..

The Symposium included a **poster session**, which encompassed a great diversity of topics. The posters were attended and discussed with the individual authors by the event's Scientific Committee members. You can go on your own virtual visit to the poster area **here**.

Miguel Antunes (with Ana Sofia Martins)

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Adalimumab Hulio	**Physicians:** rheumatologists, dermatologists and gastroenterologists, internists, paediatricians; heads of ophthalmology departments procuring Hulio.	Guide
	Patients	Safety card – adults Safety card – children 04/12/2018
Artenimol + Piperaquine Eurartesim	**Physicians:** infectious diseases and tropical medicine specialists; physicians conducting travel clinic consultations.	Information guide Pre-prescription checklist 05/12/2018
Eliglustat Cerdelga	**Physicians:** haematologists, internists, neurologists and hepatologists (gastroenterologists).	Prescriber's guide
	Patients	Alert card 26/12/2018
Leuprorelin Eligard	**Healthcare professionals:** at urology, oncology and internal medicine departments, hospital pharmaceutical services and nursing services.	Preparation instructions Preparation video 27/12/2018
Ponatinib Iclusig	**Physicians:** haemato-oncologists and haematologists. **Pharmacists**: directors of hospital pharmaceutical services and hospital pharmacists working in oncology. **Researchers** involved in clinical trials with ponatinib.	Healthcare professional brochure 06/12/2018

Medicines containing VALPROATE

VALPROATE	Target	Materials and Communications Online publication date
Oral formulations Ácido Valpróico Generis – 300 mg, 500 mg Ácido Valpróico ratiopharm – 300 mg, 500 mg Depakine – 40 mg/ml, 200 mg/ml, 300 mg Depakine Chrono 300 - 500 mg Depakine Chronosphere – 50 mg, 100 mg, 250 mg, 50-350 mg, 500 mg, 500-1000 mg, 750 mg, 1000 mg, Diplexil-R – 250 mg, 500 mg Diplexil – 200 mg, 500 mg, 200 mg/ml Diplexil-150, -300, -500, -1000	**Physicians:** neurology, psychiatry, general/family medicine, child psychiatry and neuropaediatrics.	Prescriber's guide Annual Risk Recognition Form
	Patients	Information guide Card: Contraception and Pregnancy 27/12/2018
Injectable formulations Ácido Valpróico Generis – 400 mg/4 ml Depakine – 400 mg/4 ml Diplexil 100 mg/ml Epixival – 100 mg/ml Valproato de sódio G.E.S. – 400 mg/4 ml	**Physicians:** neurology, psychiatry, general/family medicine, child psychiatry and neuropaediatrics.	Prescriber's guide
	Patients	Information guide 27/12/2018
All formulations (oral and injetable)	**Physicians:** neurology, psychiatry, general/family medicine, paediatrics and obstetrics/gynaecology. **Pharmacists** **Healthcare professionals at family planning clinics** (in health centres, hospitals and maternities).	New use restrictions; pregnancy prevention programme to be implemented 21/12/2018

Compiled by Magda Pedro

Portuguese National Pharmacovigilance System: milestones and information systems

1992 Legislative Order No. 107 of 27-07-1992

- The National Pharmacovigilance System is created and seated at the then Medicines Study Centre, in accordance with the Decree-Law Decree No. 72 of 08-02-1991 laying down the statutory definitions regarding medicinal products;
- The National Pharmacovigilance System is in charge of analyzing adverse drug reaction data reported by healthcare professionals and marketing authorization holders; a simple databse is used;
- Physicians report ADRs using a yellow card type scheme (Fig. 1);
- Marketing authorization holders use the CIOMS I template (Fig. 2) to report serious ADRs.


Fig. 1
First yellow card


Fig. 2
CIOMS I

1993 Decree-Law No. 353 of 07-10-1993

- INFARMED is created as the National Institute for Pharmacy and Medicines;
- Infarmed takes on the responsibilities of the former Medicines Study Centre;
- The National Pharmacovigilance Centre takes part in the WHO Uppsala Monitoring Centre 1st International Training Course;
- The first ADR reports are sent through to the WHO using a compatible computer template.

Fig. 3
Infarmed's logo

Fig. 4
1992-1993 ADR reporting from spontaneos sources

1997 First Pharmacovigilance Bulletin

- First issue of the quarterly Pharmacovigilance Bulletin addressing healthcare professionals;
- An English version becomes available from 1998;
- Pharmacists start reporting independently.

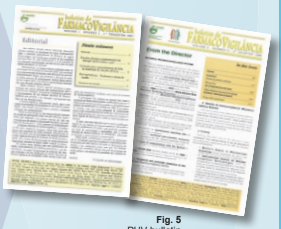
Fig. 5
PHV bulletin

1999 Ordinance No. 605 of 05-08-1999 (revoking Legislative Order No. 107 of 1992)

- The National Pharmacovigilance System bylaws are approved;
- The DrugWatch database is set up as a coherent information system following norm ICH E2B and allowing for full case entries with WHOART-coded ADRs and ICD-9-classified therapeutic indications.

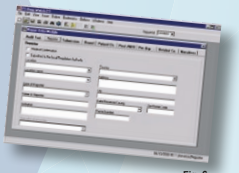
Fig. 6
DrugWatch

2000 National Pharmacovigilance System decentralization

- Northern, Central, Southern and Azores Islands Regional Pharmacovigilance Units are set up following a public tender laid out in Ordinance No. 605 of 05-08-1999;
- New ADR report cards for physicians, pharmacists and nurses, bringing the System closer to the various helathcare professional groups.

Fig. 7
PHV Units


Fig. 8
ADR notification forms

2002 Decree-Law No. 242 of 05-11-2002

- Portugal pioneers electronic ADR case transmission and is the first member state to transmit cases in XML format to EMA;
- Safety signal detection and assessment tools are thus improved.

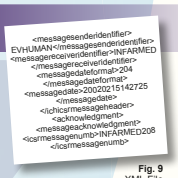

Fig. 9
XML File

2006 Decree-Law No. 176 of 30-08-2006 laying down the Medicinal Products Statute

- SVIG replaces DrugWatch as the National Pharmacovigilance System's ADR database;
- Duplicate detection and direct (from healthcare professionals) and indirect (through marketing authorization holders) source case quality verification becomes more effective;
- Regional Pharmacovigilance Units have dedicated SVIG access to enter cases;
- Electronic transmission involving marketing authorization holders begins;
- Cases are automatically sent in to EudraVigilance.


Fig. 10
SVIG

2012 ADR Portal

- Following new European legislation, consumers become able to report ADRs directly to Infarmed, to Regional Pharmacovigilance Units or to marketing authorization holders;
- An ADR Portal is set up to allow for online reporting and processing of cases received both from healthcare professionals and consumers;
- ADR Portal cases at this stage have to be sent through to the SVIG database and then forwarded into EudraVigilance.


Fig. 11
ADR Portal

2017 New ADR Portal

- Replaces the ADR Portal and SVIG databases;
- Allows for front-office online reporting and real-time access to entered cases;
- Allows for back-office report management and processing;
- Single channel to send cases through to EudraVigilance.

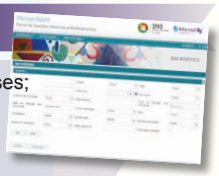
Fig. 12
New ADR Portal

Fátima Bragança, Sandra Queiroz

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics