boletim de FARMACOVIGILÂNCIA

VOLUME 22
NUMBER 6
JUNE 2018

100th BULLETIN

From the Board

This is the 100th Boletim de Farmacovigilância. In the first quarter of 1997 the Portuguese Pharmacovigilance Bulletin's first issue came out and 21 years have since gone by!

The Editorial in the Number 1 issue is still totally current: "monitoring the adverse effects of drugs once they start being used is of special relevance, and it is essential to ensure that a national pharmacovigilance system is in place that makes it possible for adverse reactions to be detected and for the benefit/risk assessment of drugs to be an ongoing process".

From 1997 to now the Portuguese Pharmacovigilance System has undergone profound changes in pursuing the goal to provide access to safer medicines at a national, European and even global level. The number of adverse drug reaction reports has increased exponentially and today both healthcare professionals and citizens in general can report adverse effects electronically by simply clicking on a link!

However, similarly to 1997, continuing benefit/risk assessment of marketed medicinal products is still of the utmost relevance to ensure that balance remains positive.

To mark the 100th anniversary we have chosen to revisit the main topics from the Number 1 issue. By doing this we also wanted to stress that, irrespective of the type of existing pharmacovigilance system, and of medicines or assessment procedures, the sole objective of this Bulletin is to keep healthcare professionals and citizens informed about the safety of the medicinal products that make up the available therapeutic arsenal.

The Board would therefore like to restate the wishes made in Boletim de Farmacovigilância No. 1: "*that this Bulletin will go on giving an effective contribution towards the protection of public health and the improvement of healthcare quality*".

Sofia Oliveira Martins

From the Director

Ever since the start of its publication back in 1997, the Boletim de Farmacovigilância has been an essential tool for the dissemination of regulatory and scientific information, not only among healthcare professionals, but also among citizens who have become more and more interested in health-related topics.

The growing number of materials to be communicated and readership interest have made it necessary to change the Bulletin from a quarterly to a monthly publication, thus speeding up the dissemination of emerging topics.

A recent study by the Spanish Medicines Agency (AEMPS) to determine which sources and means of communication healthcare professionals preferred for medicinal product safety issues clearly shows that they favour information coming from health authorities, so that biases in communicating potential health risks can be avoided.

With this in mind, we envision the future of the Boletim de Farmacovigilância as a publication on the safety of medicines that is a national reference for all those who directly or indirectly deal with medicinal products, either as professionals or as consumers.

In this **100th issue of the Boletim de Farmacovigilância** we celebrate Portuguese pharmacovigilance, which has always benefitted from the Bulletin's reputation. We also celebrate its Editor's merit who first started the Boletim in 1997 and whose dedication and professionalism account for the publication's unanimously recognized prestige. For all this we are thankful to Dr Rui Pombal and look forward to the 200th issue!

Fátima Canedo

INDEX CARD

Director: Fátima Canedo
Editor: Rui Pombal
Contributors: Ana Severiano, Ana Sofia Martins, António Leandro Ponte, Cristina Mousinho, Elsa de Fátima Costa, Fátima Bragança, Fátima Hergy, Leonor Nogueira Guerra, Magda Pedro, Márcia Silva, Miguel Antunes, Sílvia Duarte, Vanda Araújo
Publishing Assistant: Inocência Pinto
Advisory Board: Conselho Diretivo do INFARMED, I.P.
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Phone: +351 217 987 100
E-mail: infarmed@infarmed.pt
Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

From the Editor

From a hardcopy to an exclusively digital format, from a Portuguese to a bilingual version, from quarterly to monthly publication, the safety topics contained in the Boletim de Farmacovigilância since 1997 number several hundred. At the end of the first semester of 2018 one could look up in the Bulletin's online index 1,033 different active ingredients. Another few hundred drugs should be added to the tally which, though not the subject matter of Boletim articles proper, are highlighted in sections such as the former *Drugs under Study* or, more recently, *Educational Materials* and *Communications to Healthcare Professionals*. The latter are sections that lead interested readers on to detailed safety documentation by clicking on a link.

Now at the one-hundredth Bulletin, after 76 editorials and 502 articles, we look forward to the future as we look back to the long and exciting story of this publication. The editorials on the previous page from the Portuguese Medicines Authority Board of Directors and from the Medicines Risk Management Department Director underline the fact that the Boletim de Farmacovigilância has always sought to support and keep up with the developments of the Portuguese national pharmacovigilance system as a forefront tool for the communication and dissemination of medicines safety information to healthcare professionals in this country.

All this would not have been possible without the relevance and encouragement provided by the Portuguese medicines agency to the Bulletin since its very inception, and the untiring work of many dozens of contributors, both occasional and regular, both in-house and guest authors. Working with all of them has been a continuing source of learning and a huge privilege for the Editor. My sincere thanks to:

Contributors (article authors)

Adriana Gamboa **A**lexandra Pêgo **A**na Araújo **A**na Gonçalves **A**na Marta Anes
Ana Peres **A**na Rita Lopes **A**na Severiano **A**na Sofia Martins **A**nabela Lima
António Faria Vaz **A**ntónio Leandro Ponte **A**ntónio Lourenço
Beatriz Tavares da Costa **C**arlos Matos Dias **C**atarina Costa **C**atarina Godinho
Catarina Martins **C**ecília Lima **C**láudia Bicho **C**onceição Sobral
Cristina Mousinho **C**ristina Rocha **C**ristina Sampaio **E**lsa de Fátima Costa
Eugénio Teófilo **E**va Rebelo Gomes **F**átima Bragança **F**átima Canedo
Fátima Hergy **F**átima Vaz **F**ernanda Marques **F**rancisco Batel Marques
Henrique Luz Rodrigues **I**nês Clérigo **I**nês Ribeiro Vaz **I**sabel Borba Vieira
Isabel Brito Afonso **I**sabel Sobral **I**sabel Tavares **J**oana Isabel Marques
Joana Oliveira **J**oão Ribeiro da Silva **J**orge Polónia **J**osé Sequeira
Leonor Chambel **L**eonor Nogueira Guerra **L**uís Pinheiro **M**adalena Arriegas
Madalena Melo **M**agda Pedro **M**árcia Silva **M**argarida Guimarães
Maria do Rosário Pereira Rosa **M**iguel Antunes **P**ascal Demoly **P**aula Broeiro
Paula Roque **P**edro Marques da Silva **R**egina Carmona **R**icardo Cruz Correia
Rita Dias **S**andra Queiroz **S**ílvia Duarte **S**ílvia Mota Gomes **S**ofia Borges
Sofia Guimarães **S**usana Gonçalves **S**usana Prisca **T**elma Rijo **T**eresa Herdeiro
Teresa Santos Dias **V**anda Araújo **V**asco Maria

Rui Pombal

Fluoroquinolones: 1997-2018

Fluoroquinolones are still one of the most prescribed groups of antibiotics worldwide. Their broad spectrum of therapeutic indications is certainly a factor, together with their long experience of use.[1]

More than twenty years since the Boletim de Farmacovigilância was first published including an article on cases of tendinitis and Achilles's tendon rupture,[2] the safety profile of fluoroquinolones remains a focus of attention for regulatory authorities. An example of this is the change approved on 13th June 2014 to the Summary of the Product's Characteristics and the Patient Information Leaflet concerning fluoroquinolones for systemic use and an association with **retinal detachment**, a rare but very serious effect.[3]

INFARMED
INSTITUTO NACIONAL DA FARMÁCIA E DO MEDICAMENTO
MINISTÉRIO DA SAÚDE

boletim de FARMACOVIGILÂNCIA
VOLUME 1. NÚMERO 1. 1.º TRIMESTRE 1997

Editorial

Nas últimas décadas têm-se observado desenvolvimentos notáveis na descoberta de novos medicamentos. Hoje, o crescente aparecimento de fármacos de origem biotecnológica tem trazido para a ordem do dia a avaliação benefício/risco de cada medicamento e a necessidade da sua adequada monitorização, em face da sua cada vez mais rápida introdução no mercado.

Efectivamente, os ensaios clínicos realizados antes da autorização de introdução no mercado (AIM), não envolvem um número elevado de doentes, nem decorrem em períodos suficientemente longos, que permitam a detecção de todos os efeitos adversos do medicamento. Muitos destes efeitos apenas surgem após a sua efectiva e generalizada utilização nas mais diversas situações clínicas.

Neste contexto, assume especial relevância a monitorização dos efeitos adversos dos medicamentos após o início da sua utilização, tornando-se fundamental garantir o funcionamento de um Sistema Nacional de Farmacovigilância que permita a sua detecção e permanente avaliação do seu benefício/risco.

A Farmacovigilância desempenha, assim, após a concessão da autorização de introdução no mercado do medicamento, uma função essencial para a correcta e adequada utilização dos medicamentos.

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pete o seu tratamento e avaliação, com o apoio da Comissão de Farmacovigilância.

A participação dos médicos no sistema tem vindo a aumentar de forma muito positiva, verificando-se que no 1.º semestre do corrente ano foi já recebido no INFARMED igual número de notificações ao recebido em 1996. É necessário, no entanto, criar uma forma adequada de comunicação entre o CNF e os profissionais de saúde que, sem prejuízo de ser complementada com contactos mais directos, assegure o

More recently, a safety review promoted by EMA,[4] and which is still ongoing, is aiming to analyse in detail the duration of serious **muscle, joint or neurological** adverse effects arising from the use of (fluoro)quinolones for systemic use and for inhalation (the following are marketed in Portugal: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, and prulifloxacin).

On 10th July 2018, the US Food and Drug Administration (FDA) issued a safety communication regarding a known potential risk of **hypoglycaemic effects**, which can be severe in elderly and diabetic patients, as well as a risk of **transient mental disorders**, such as attention disorder, disorientation, agitation, nervousness, memory loss and delirium.[5] This communication further stressed the need for patients to be correctly identified for whom fluoroquinolones should be avoided and therapeutic alternatives sought.

The history of fluoroquinolone safety from 1997 to the present day is a case in point of how the safety profile of a medicine is not static, rather undergoes continuing observation and analysis on the part of medicines authorities and other players of the pharmacovigilance system.

Miguel Antunes

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Adverse Drug Reactions in Portugal 2017/1997: Who Reports/ed What?

In 1997, the first in-depth article in the Boletim de Farmacovigilância made a qualitative and quantitative analysis of the spontaneous adverse drug reaction (ADR) reports received by the then National Pharmacovigilance Centre between 1st January 1993 and 15th June 1997. At the time, reports were possible only from physicians and the pharmaceutical industry.[1]

As in 1997, still today "early marketing of novel drugs precludes full knowledge of their safety profile, namely in long-term use, in extreme age groups and in persons with comorbidities" [1]. Spontaneous reporting systems are very important in that they allow for safety signals to be generated early on.[2] Between July 2013 and December 2016 only, fourteen medicinal products have been withdrawn, revoked or suspended from the European market for safety reasons.[3]

We now revisit the study undertaken in 1997 with data from 2017. The steep increase in the number of spontaneous reports received in the last few years explains why in the Broeiro[1] study a mere **243 reports** in almost four and a half years were analysed, whereas in the year 2017 only, as many as **2,650 reports** were submitted directly by healthcare professionals and consumers. The comparative results follow:

- In 1997 only physicians could report ADRs. In 2017 reports came from **physicians** (1,201 reports, 45% of total), as well as from **pharmacists** (894, 34%) and **nurses** (235, 9%). **Consumers** sent in 277 reports (10%).
- The district of **Porto** comes first in rate of ADRs per million inhabitants (377), followed by **Lisbon** (305) and the group made up of the districts of **Coimbra, Aveiro and Leiria** (267). Twenty-one years ago, though most ADRs came from the Lisbon and Tagus Valley (44%) and Northern (30%) regions, the highest ADR reporting rate was found in the Alentejo region (56 per million).
- The medical speciality that reported most in 2017 was **Immunology and Allergy** (35%), followed by **Dermatology** (12%) and **Rheumatology** (11%). General/Family Medicine was ahead with 72% of reports in 1997 and comes now fifth with 7% of all reports from physicians. Interestingly, Dermatology remains in second place for the specialities that send in the most ADR reports.
- Patients suffering ADRs were mostly **female** (54%) and aged between **18 and 64 years** (40%). In 1993-97 females were also predominant (64%) but the age group with the most ADR cases (33%) was that of patients aged 65 or older.
- The most frequent organ systems involved in ADRs were **general or site of administration disorders** (31%), followed by **skin** (28%), **gastrointestinal** and **neurologic** (18% and 16%, respectively). Not very differently, in 1993-97 the top ADR categories were skin (39%), followed by GI and neurologic (13% each).
- The most frequent pharmacological groups involved in ADRs in 2017 were **antineoplastic agents** (13%), followed by **immunosuppressants and antibiotics for systemic use** (11% each). This is rather different from the last century, when antibiotics (31%), NSAIDs (15%) and antihypertensive agents (13%) predominated.

In brief:

- Physicians remain the main source of ADR reports.
- Females remain the most affected gender (they are also the gender using the most medicines).
- Skin, GI and neurologic ADRs have consistently stayed among the most frequent types of reactions.
- Antibiotics were and still are very relevant as a pharmacological group involved in ADRs. However, in 2017, mirroring developments in the therapeutic armamentarium, new pharmacotherapeutic drugs such as antineoplastic and immunosuppressant agents have acquired greater notoriety.

The conclusions from the Broeiro[1] study remain generally current and the spontaneous ADR reporting system still reveals "significant morbidity and mortality ascribed to adverse reactions, which further underscores the importance of pharmacovigilance and ADR reporting in particular".

Miguel Antunes

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