

PGEU Best Practice Paper:
Pharmacovigilance and
Risk Minimisation

Ref 17.09.26E 003



PGEU GPUE

**Pharmaceutical Group
of European Union**

Table of Contents

Executive Summary	3
Glossary	4
1. Pharmacovigilance	5
Pharmacovigilance: A New Science is Born.....	5
Recent Developments	5
Objectives of this Best Practice Paper	6
Pharmacovigilance and Risk Minimisation in Europe	6
2. Pharmacists' Role in Pharmacovigilance	10
Pharmacists and Pharmacies	10
Adverse Drug Reactions, Drug-related Problems and Adherence.....	11
Interactions	15
Duplication	17
Special Patient Populations	17
Reclassification of Medicines	19
Quality Control, Restrictions, Recalls and Withdrawals.....	20
electronic Health Records (eHRs)	22
Abuse.....	24
Off-label Use.....	24
3. PGEU's Work on Pharmacovigilance	26
EMA's Healthcare Professionals' Working Party (HCP/WP)	26
EMA Pharmacovigilance Risk Assessment Committee (PRAC)	27
EMA HCP/WP Topic Group on Risk Minimisation Measures	27
4. Conclusions and Recommendations	28
Conclusions.....	28
Recommendations.....	28



The Pharmaceutical Group of the European Union (PGEU) is the association representing community pharmacists in 31 European countries. In Europe over 400.000 community pharmacists provide services throughout a network of more than 160.000 pharmacies, to an estimated 46 million European citizens daily.

PGEU's objective is to promote the role of pharmacists as key players in healthcare systems throughout Europe and to ensure that the views of the pharmacy profession are taken into account in the EU decision-making process.



Executive Summary

This best practice paper outlines the evolution of pharmacovigilance in Europe, particularly in the context of the fifth anniversary of the 2012 EU pharmacovigilance legislation and recent developments in the field. Additionally, this paper describes the varied role of community pharmacists in ensuring the safe, effective and rational use of medicines in practice. Furthermore, this paper highlights PGEU's work on pharmacovigilance and risk minimisation measures and provides an overview of best practices from PGEU member organisations.

As the experts in medicines, the most accessible group of healthcare professionals in Europe and often the last professional a patient sees before taking a medication, community pharmacists are profoundly implicated in aspects related to pharmacovigilance, medication use and patient safety.

The broad and diverse areas explored in this paper include prevention and reporting of adverse drug reactions, implementation and adherence to risk minimisation measures in practice, minimisation of medication errors and prevention of drug interactions. Additionally, the paper outlines the use of Good Pharmacy Practices and protocols, the safe use of medicines during pregnancy and breastfeeding and safe use in high risk or particularly vulnerable patient groups. The paper also highlights how community pharmacists improve adherence and promote the most effective use of medications and the use of innovative technologies to enhance patient safety and high quality of care.

As a consequence, the PGEU makes several recommendations in order to maximise the potential contribution community pharmacists can make to pharmacovigilance and risk minimisation activities. They are as follows:

1. Patient-facing pharmacy services that support the safe, effective and rational use of medicines are beneficial in minimising risk (e.g. medication review and new medicine services) and should be expanded and supported by policy makers and health systems payers;
2. Where feasible, pharmacists should have access to shared electronic health records to ensure continuity of care and reduce the risks of adverse drug reactions, medication errors, interactions and other harmful events;
3. Indications should be communicated to pharmacists (e.g. on the prescription) to ensure the most effective and appropriate therapy and counseling is provided, as well as to ensure the correct reporting of suspected adverse events from the use of medicines off-label;
4. Further interdisciplinary collaboration is welcomed between pharmacists and other healthcare professionals to maximise the benefits for patient safety (e.g. more effective problem solving and prevention of adverse events in partnership, continuity of care, reduced costs and administrative burden);
5. Continued collaboration between national pharmacy associations and national medicines agencies and the PGEU and the European Medicines Agency is welcomed to further strengthen and support the role and contribution pharmacists can make to patient and medication safety;
6. Relevant authorities and organisations are incorporating good pharmacovigilance practices, risk minimisation measures and medication safety activities into Good Pharmacy Practices, standard operating procedures, institutional protocols, continuous education, continuous professional development and pharmacy education and training. Such incorporation should be encouraged and supported.



Glossary

ADR	Adverse Drug Reaction	MAH	Marketing Authorisation Holder
CE	Continuing Education	ME	Medication Error
CPD	Continuous Professional Development	MEEG	Medication Error Working Group
CHMP	Committee for Human Medicinal Products	MR	Medication Review
CPME	Standing Committee of European Doctors	NMS	New Medicine Service
DP	Dossier Pharmaceutique	OTC	Over the counter
DPP	Dossier Pharmaceutique Partargé	PASS	Post-authorisation Safety Study
DRP	Drug-related Problem	PGEU	Pharmaceutical Group of the European Union
EC	European Commission	PMR	Patient Medication Record
eHR	Electronic Health Record	PPP	Pregnancy Prevention Programme
EMA	European Medicines Agency	PRAC	Pharmacovigilance Risk Assessment Committee
EU	European Union	PTAM	Pharmacotherapy Audit Meeting
FMD	Falsified Medicines Directive	RMM	Risk Minimisation Measure, aRMM Additional Risk Minimisation Measures
GP	General Practitioner	RMP	Risk Management Plan
GPP	Good Pharmacy Practice	SCR	Summary Care Record
GvP	Good Pharmacovigilance Practice	SOP	Standard Operating Procedure
HCP	Healthcare Professional	SmPC	Summary of Product Characteristics
HCP/WP	Healthcare Professionals' Working Party	TG	Topic Group
HSE	Health Service Executive (of Ireland)	WHO	World Health Organisation
ICT	Information Communication Technology		



1. Pharmacovigilance

Pharmacovigilance: A New Science is Born

More than 10.000 children were born with congenital malformations following exposure to thalidomide in Europe, Australia and Japan after its introduction in the 1950's to treat pregnancy-associated nausea¹. This tragedy triggered the first systematic efforts to test and assess medicines for signs of toxicity both prior to and after marketing authorisation. Thus, the science of pharmacovigilance was born.

Legislation concerning pharmaceuticals in the EU is more than 50 years old and its initial conception was deeply linked with the effects of thalidomide and the need for no medicine to be marketed ever again in the EU without prior authorisation².

Medicines regulators established review processes to evaluate suspected adverse drug reactions (ADRs) from clinical trials, from marketing authorisation holder (MAHs) databases, spontaneous reports from healthcare professionals (HCPs), patients and from the scientific literature.

Recent Developments

No medicine is 100% safe or free of risks and despite the concerted efforts of medicines regulators to ensure medicines are taken and used as safely as possible, recent events justify the need to be vigilant and for robust methods of testing and authorisation of medicines. For example, the anti-inflammatory rofecoxib (Vioxx®) was withdrawn from the global market in 2004 following evidence that long-term use significantly increased the chances of suffering serious cardio-vascular events³.

The anti-diabetic benfluorex (Mediator®) was subject to several reviews, restrictions on its use and individual withdrawal from several Member States before its eventual

European withdrawal in 2009 as a result of its benefits no longer outweighing its risks⁴. The anti-nausea and sickness medication domperidone (Motilium®, which is also available as a non-prescription medicine in some Member States), was recently reviewed by the EMA with restrictions placed on its use as a result of evidence concerning the risk of arrhythmias and changes to the electrical functioning of the heart⁵. Moreover, evidence for effects of entire classes of medicines (e.g. non-steroidal anti-inflammatory medicines – NSAIDs) continues to evolve and as such, the European regulatory and health communities continually evaluate their use where needed.

The year of 2017 marks the fifth anniversary of the 2012 revisions to the European pharmacovigilance legislation, the most significant of which gave rise to the formal establishment of the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC)⁶ and recognition that reporting of ADRs is an obligation for all HCPs, including pharmacists. Following this, the 2013 revisions to the European Directive on the recognition of professional qualifications included reporting of ADRs as an activity for pharmacists to pursue across Europe⁷.

At both national and European levels competent authorities (medicines regulators) review evidence of suspected ADRs and medication errors (MEs). At European level, it is the PRAC which performs such assessments. PRAC is comprised of the national medicines regulators from across the EEA, in addition to independent scientific experts and representatives from patients and healthcare professionals. PGEU has consistently advocated for a representative of practising HCPs to be a nominated member of the PRAC and as such has successfully provided two practising community pharmacists to sit on PRAC since its inception. There has been a succession of referrals concerning highly teratogenic medicines in recent

1 Kim JH. And Scialli AR. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. *Toxicological Sciences*. 2011;122(1):1–6. doi:10.1093/toxsci/kfr088
2 https://ec.europa.eu/health/human-use/50years_en
3 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000352.jsp&mid=WC0b01ac058004d5c1

4 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Benfluorex/human_referral_000220.jsp&mid=WC0b01ac05805c516f
5 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Domperidone-containing_medicines/human_referral_prac_000021.jsp&mid=WC0b01ac05805c516f
6 Commission Implementing Regulation (EU) No 520/2012 and Regulation (EU) No 1027/2012 amending Regulation (EC) No 726/2004
7 Directive 2013/55/EU amending Directive 2005/36/EC



years (e.g. retinoids and valproate), both of which are regularly dispensed in community pharmacies. As such, this paper is timed to raise awareness of the role that community pharmacists play in safeguarding the use of medicines in Europe.

Objectives of this Best Practice Paper

Pharmacists, with extensive education and training in pharmacology, pharmacotherapy, toxicology and pharmaceutical care are regarded as the experts in medicines and their use. Additionally, the community pharmacy and pharmacist network across Europe results in community pharmacists being the most accessible group of healthcare professionals across Europe. Often the last person a patient sees or consults with before taking a medication is a community pharmacist. Despite these facts, more can be done by health policy makers and health systems payers to enhance the role of community pharmacists and their contribution to pharmacovigilance and patient safety activities.

As such, this paper has been drawn-up as a direct response to the above issues in order to address the following objectives:

1. Collection and exchange of selected best practices concerning pharmacovigilance and medication safety from pharmacists across Europe;
2. Awareness raising of the role community pharmacists play in the safe use of medicines to EU institutions and agencies active in the use of medicines;
3. Awareness raising of the role community pharmacists play in the safe use of medicines to other appropriate authorities and organisations.

Pharmacovigilance and Risk Minimisation in Europe

Definitions

The EMA is a decentralised agency of the EU, established in 1995, which is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. The EU pharmacovigilance legislation defines pharmacovigilance as:

“ *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem.*”

The EU pharmacovigilance legislation also defines a medication error (ME) as:

“ *an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.*”

This definition includes errors concerning the prescribing, dispensing, storing, preparation and administration of a medicine. The ME definition is included in this paper as MEs are the most common cause of preventable ADRs.

Pharmacovigilance Throughout the Lifecycle of Medicines

During the pre-authorisation research and development phase of a medicine's lifecycle, clinical trial sponsors (i.e. the pharmaceutical industry, researchers) are required to submit reports of suspected serious ADRs to the 'EudraVigilance' system. This is an electronic system for handling and analysing information on suspected ADRs to medicines in the European Economic Area.

At the point of application for marketing authorisation, applicants need to submit a risk management plan (RMP) as part of their application. RMPs include current knowledge of the safety of a medicine and proposed pharmacovigilance activities for



future surveillance. They are designed to further monitor the safety of the medication throughout its lifecycle.

Following marketing authorisation approval and launch of the medication (and subsequent use by patients), the MAHs, national competent authorities for medicines and the EMA follow numerous detailed pharmacovigilance processes. They include those covering risk management strategies, Good Pharmacovigilance Practices, incident management plans, medical literature monitoring, medication errors, medicines under additional monitoring, periodic safety update reports, pharmacovigilance systems, post-authorisation safety studies, regulatory and procedural guidance and 'signal' management.

In the context of the post-authorisation phase of the medicine's lifecycle, patients and healthcare professionals are encouraged and obliged (respectively) to report suspected ADRs to the MAHs or national competent authorities.

These 'signals' are investigated and collated with other similar signals at national and European level in order to establish if they constitute an ADR. Depending on the type, severity, disease state, medication class and use in practice, the national competent authorities and the EMA (PRAC and the Committee for Human Medicinal Products, CHMP) may issue advice, communications, recommendations, referrals, additional monitoring, Good Pharmacovigilance Practices, educational materials, restrictions, further studies or even withdrawal of the medicine. Good Pharmacovigilance Practices are explained further below given their relevance for practicing HCPs and patients using medicines.

Good Pharmacovigilance Practices and Risk Minimisation Measures

Good Pharmacovigilance Practice guidelines (GvPs) are published by the EMA in order to guide MAHs and EU/national regulatory authorities on various aspects of pharmacovigilance to improve its performance in Europe. Of particular relevance to HCPs (including community pharmacists) is the guideline on risk minimisation and medication errors. This guideline deals with issues concerning the medicine's use and other practical elements such as naming, labelling, communication with HCPs/patients, educational materials and tools to aid the prevention of ADRs/MEs in practice.

One element of GvP guidelines are Risk Minimisation Measures (RMMs), which are developed prior to the launch of a medicine. Following launch of a medicine, the regulators may consider it necessary for revision of the implementation and adherence to RMMs. Furthermore, additional RMMs (aRMMs) can be introduced if evidence arises that the existing RMMs are not sufficient following the authorisation of the medicine. The EMA's GvP "Module XVI" (*RMMs: selection of tools and effectiveness indicators*) consists of a selection of additional procedures and materials for use in practice such as educational materials for HCPs and patients, prescriber checklists, dispensing guides etc.

Community pharmacists are a key stakeholder in the development of, implementation of and adherence to RMMs in practice, both in terms of prescription medications, but also to their role in the stewardship of the safe use of non-prescription medicines. In the following two pages there are two case studies outlining the elements of RMMs in practice, with an example of one of the materials for use (a dispensary poster).



UK Case study: isotretinoin (example of Pregnancy Prevention Programme (PPP) content)⁸

PPP consists of three parts:

1. Educational programme
2. Therapy management
3. Distribution control

The purpose of the educational programme is to:

- Enhance the understanding of the teratogenic risks of Isotretinoin by both patients and physicians
- Enhance female patient information, awareness and acknowledgement

1. As part of the educational programme the following brochures are provided:

- Physician's Guide to Prescribing Isotretinoin
- Physician's Checklist for Prescribing to Female Patients
- Pharmacist's Guide to Dispensing Isotretinoin
- Acknowledgement Form for Female Patients
- Patient Information Brochure
- Brochure on Contraception

2. The basic components of therapy management in the Isotretinoin PPP are:

- Provision of educational material to patients
- Medically supervised pregnancy testing before, during and 5 weeks after end of treatment
- Use of at least one method of contraception and preferably 2 complementary forms of contraception including a barrier method for at least one month before initiating therapy, continuing throughout the treatment period, and then for at least one month after stopping therapy

3. Under the Pregnancy Prevention Programme the prescription of Isotretinoin should be limited to a 30-day supply. In addition the prescription for Isotretinoin is only valid for 7 days.

⁸ <http://www.medicines.org.uk/emc/medicine/32477>

UK Case study: sodium valproate (example of materials provided for use in pharmacy)⁹

Communication to Pharmacist



Letter to Pharmacists

Educational Materials for Pharmacist



HCP Card



HCP Booklet

Prompts/Reminders in the Pharmacy



Dispensary Shelf Sign



Dispensary Poster

Educational Materials for Patient



Patient Card



Patient Guide

⁹ <http://www.medicines.org.uk/emc/medicine/23020>



An example of one of the tools for use in practice in the UK can be seen below (dispensary poster for valproate)¹⁰.

FOR DISPENSARY USE ONLY

WARNING ON USE OF VALPROATE



THE RISK – WHO AND WHAT

Valproate should only be used in girls, women of child bearing age and those who are pregnant or planning pregnancy, when other treatments are ineffective or not tolerated.

Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and congenital malformations (in approximately 10% of cases).

To support effective practice, *Valproate Patient Cards* and *Valproate Patient Guides* are available for you to provide to female patients taking valproate.

These materials highlight the risks of taking valproate whilst pregnant and remind patients use effective contraception and to see their prescriber urgently should they be planning, or become, pregnant.

ACTION FOR THE PHARMACIST/PHARMACY STAFF

- ✓ When dispensing any valproate preparation to female children, female adolescents, women of childbearing potential or pregnant women **CHECK** that their prescriber has discussed the risks of in utero exposure with them and they are aware of these.
- ✓ If the prescriber **HAS NOT DISCUSSED** the risk with the patient, contact the prescriber and remind them of their responsibility to do so and ask them to arrange an urgent follow-up appointment with the patient.
- ✓ **PROVIDE** a *Valproate Patient Card* every time you dispense a valproate preparation to female children, female adolescents, and women of childbearing potential or pregnant woman.
- ✓ **ASK** if they have received a *Valproate Patient Guide* (booklet), and if not provide a copy.
- ✓ **ADVISE** to always use contraception and to see their prescriber urgently should they be planning, or become, pregnant.



Copies of the *Valproate Patient Guide* and *Valproate Patient Cards* can be ordered, at no cost, by contacting Sanofi Medical Information on **0845 372 7101** or by emailing UK-medicalinformation@sanofi.com

The *Patient Guide* and *Cards* can also be downloaded from the EMC website **www.medicines.org.uk** where it will be found linked with entries for medicines containing valproate.

CALL FOR REPORTING
▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your patients may get. See www.mhra.gov.uk/yellowcard for how to report side effects.

June 2017
SAGB.VPA.17.05.0570

¹⁰ <http://www.medicines.org.uk/emc/medicine/23021>



2. Pharmacists' Role in Pharmacovigilance

Pharmacists and Pharmacies

Accessibility

Community pharmacists are often the last professional to have contact with a patient or their carer before a medication is used. This provides a unique opportunity for an expert in the use of medicines (the community pharmacist) to provide information, advice and support for the safe, effective and rational use of a medicine at the final point before use. Additionally, no appointment or co-payment is needed to consult a pharmacist for information on medicines and pharmacies can be accessed 24/7, all year round with extended opening hours and on-call services. As such, community pharmacists are excellently placed to provide support for people taking medicines.

Pharmacist-patient relationship

Located in the heart of communities, pharmacists often establish long-term relationships with their patients and local populations. Additionally, pharmacies across Europe are extending and opening private consultation areas to further enhance the quality of pharmaceutical care and information on medicines provided.

Education and Training

In Europe, pharmacists must complete a minimum of five years of education and training to become a pharmacist. Throughout this period of training and education, pharmacy students cover all stages of a medicine's lifecycle from initial discovery and development to post-marketing surveillance and pharmacovigilance. Pharmacists are exposed to a unique mix of disciplines during their education and training including scientific, regulatory and clinical elements.

Additionally, the European Directive on the recognition of professional qualifications¹¹ includes a number of activities which pharmacists perform in practice, specifically that they:

- Provide information and advice on medicinal products, including their appropriate use;
- Report adverse reactions of pharmaceutical products to competent authorities;
- Provide personalised support for patients taking medication.¹²

Expert Knowledge of Medicines

Pharmacists are the experts in medicines, both prescription and non-prescription medicines. In addition to undergraduate education and training focusing on the development and use of medicines, community pharmacists are also committed life-long learners across Europe. Community pharmacists participate in continuous professional development activities (CPD) and continuous education (CE) relevant to their role in order to keep their knowledge up-to-date, particularly on advances in medicines use and pharmacotherapy¹³.

Thus, community pharmacists are competent in the use of medicines and are an appropriate HCP to ensure the safe, effective and rational use of medicines, including preventing and reporting of ADRs.

Community pharmacists' activities relevant to pharmacovigilance can be summarised under the following themes:

- Prevention, reporting and resolving ADRs and drug-related problems (DRPs), interactions, duplications and promoting rational use;
- Special cases relevant to off-label use;
- Caring for vulnerable patient groups (e.g. pregnant, elderly);
- Special cases relevant to non-prescription medicines;
- Quality control and participation in recalls and withdrawals.

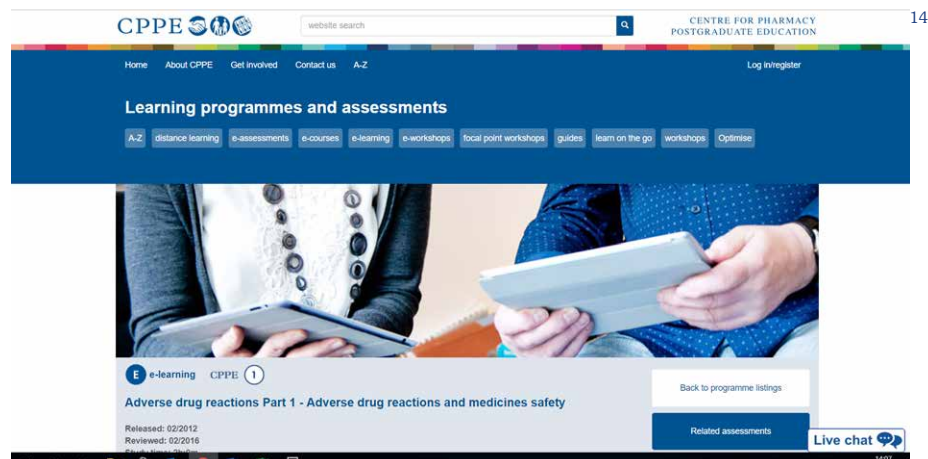
11 Directive 2013/55/EU amending Directive 2005/36/EC

12 Directive 2013/55/EU amending Directive 2005/36/EC §45 para 2 g-i

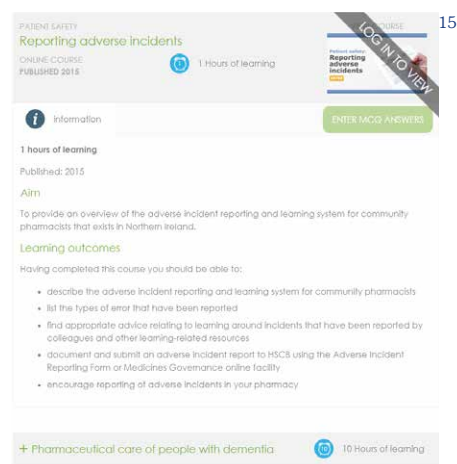
13 https://ec.europa.eu/health/sites/health/files/workforce/docs/cpd_mapping_report_en.pdf



In the examples below, online access to CPD materials by the UK Centre for Pharmacy Postgraduate Education concerning ADRs is available for pharmacists, often developed in close collaboration or by pharmacist/pharmacy associations.



14



15

14 <https://www.cppe.ac.uk/programmes/1/adr1-e-01/>
15 <https://www.nicpld.org/courses/?programme=pharmacist&coursetype=ol&show=allusers>

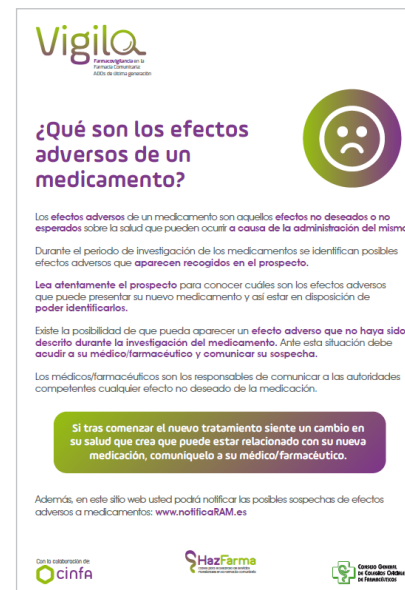
Adverse Drug Reactions, Drug-related Problems and Adherence

Community pharmacists, with their expert knowledge of both the development and use of medicines, their location, accessibility and opportunities to establish rapport with their patients, are well placed to prevent, report and mitigate suspected ADRs, DRPs and MEs. Community pharmacists are often an under-utilised resource in European health systems and there is significant potential for greater prevention, reporting and management of ADRs, by community pharmacists, particularly in the context of medicines with a particularly high risk or medicines under additional monitoring.

In the examples below, the General Council of Spanish Pharmacists produced educational materials on the pharmacovigilance system for both community pharmacists (left) and their patients (right).



16 <http://www.portalfarma.com/>



16



Additionally, some Member States have established collaboration or committees at local level mirroring a format similar to PRAC in order to discuss medication safety-related topics, for example in Bulgaria and Germany, where one member of the committee must be a pharmacist.

Medicines Under Additional Monitoring ▼

Medicines under additional monitoring (i.e. those that are more closely scrutinised by regulatory authorities in Europe) include nationally and centrally authorised products in the following groups:

- Medicines containing a new active substance (not previously contained in any authorised medicine in the EU);
- Biological and biosimilar medicines (authorised after 1st January 2011)¹⁷;
- Medicines which are subject to post-authorisation safety studies (PASS);
- Medicines with conditional approval / authorised under exceptional circumstances;
- Medicines authorised with specific suspected ADR recording / monitoring obligations.

They are identified in practice by an inverted black triangle ▼ on their package leaflet and Summary of Product Characteristics (SmPC) and remain on this list for at least five years¹⁸. At the point of dispensing, pharmacists utilise the black triangle symbol as a trigger to start a dialogue with the patient about preventing, mitigating and reporting ADRs and MEs by providing advice and information on how to take the medicine most effectively and what to do in the event of a suspected ADR or ME.

17 This is of particular relevance given the rapidly increasing number of biological and biosimilar medicines which are being dispensed in community pharmacies with requirements for traceability of batch/lot numbers by pharmacists.
18 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150608.pdf

In the examples below, the French Chamber of Pharmacists' professional bulletin and journal alerts pharmacists to restrictions and cautions concerning a medication under additional monitoring and with a PPP (for females of child-bearing potential (FCBP)). Sodium valproate (and related substances) can cause significant effects on the foetus' development and should generally be avoided by FCBP unless under specialist advice.

Contre-indication des médicaments à base de valproate utilisés en psychiatrie chez la femme enceinte et la femme en âge de procréer sans contracept...

Médicament Valproate

Cette nouvelle mesure prise par l'ANSM, effective au 7 juillet 2017, vise à ne plus exposer d'enfants aux risques d'un traitement par valproate au cours...

> Lire l'article



19

20

ENQUÊTE
VALPROATE ET DÉRIVÉS:
VOTRE ENGAGEMENT
AUPRÈS DES PATIENTES

L'enseignement tiré d'un récent sondage est manifeste : les nouvelles conditions de prescription et de délivrance (CPD) du valproate et de ses dérivés sont peu connues par les patientes, à la différence des pharmaciens, qui considèrent bien les maîtriser pour 80 % d'entre eux*.

Pour rappel, les nouvelles CPD s'appliquent à toutes les patientes depuis le 31 décembre 2015. Compte tenu du risque lié à l'utilisation de ces médicaments pendant la grossesse, les jeunes filles, adolescentes et femmes en âge de procréer doivent recevoir toute l'information nécessaire et signer un accord de soins avant de commencer ou de renouveler leur traitement par valproate ou ses dérivés.

Le rôle central du pharmacien
Soyez-vous de minimiser les risques liés à ces médicaments, le pharmacien a un rôle central au travers de différentes actions :

- vérifier la conformité de l'ordonnance initiale actuelle et l'accord de soins.
- La non-présentation de ces documents par une patiente doit être gérée au cas par cas. Devant une initiation de traitement, la délivrance pourra être refusée. Pour un renouvellement, l'information sur le risque en cas de grossesse devra être rappelée systématiquement de même que l'importance de ne pas arrêter brutalement le traitement. Une quantité minimale de traitement pourra, à titre exceptionnel, être dispensée (un mois de traitement). Dans tous les cas, un contact auprès du prescripteur devra être envisagé.

• rappeler la nécessité d'utiliser une contraception efficace pour les femmes concernées ;

• remettre la brochure d'information en cas de besoin (échangeable sur les sites Internet des laboratoires pharmaceutiques concernés ou sur celui de l'Agence nationale de sécurité du médicament et des produits de santé) ;

• rappeler la nécessité de consulter un médecin en cas de désir de grossesse.

* Enquête "Vigilance menée auprès des pharmaciens représentés de six pharmacies du 22 au 28 octobre 2015."







19 <http://www.ordre.pharmacien.fr/Communications/Les-actualites/Contre-indication-des-medicaments-a-base-de-valproate-utilises-en-psychiatrie-chez-la-femme-enceinte-et-la-femme-en-age-de-procreer-sans-contraception-efficace>
20 http://www.ordre.pharmacien.fr/content/download/251055/1368503/version/4/file/CNOP054_ok.pdf



Another example shows how the Association of Pharmacists in Belgium makes product-specific relevant pharmacovigilance information available at the point of dispensing. A webservice integrated into pharmacy dispensing software alerts pharmacists that a medication is subject to additional monitoring ▼, as well as to existing DHPC's and educational materials as part of the RMP.

XARELTO 20 MG COMP PELL 98 X 20 MG (2888683) - BAYER PHARMACEUTICALS

Ce produit dispose des données de pharmacovigilance suivantes:

 Médicament pour lequel on applique des activités supplémentaires de minimisation des risques > Cliquez ici	 Qu'est-ce que cela signifie?
 Médicament avec communication directe envoyée aux professionnels de la santé > Cliquez ici	 Qu'est-ce que cela signifie?
 Médicament sous surveillance supplémentaire Black Triangle > Cliquez ici	 Qu'est-ce que cela signifie?

Importance of Real-world Data

Real-world data is data collected from actual practice scenarios, i.e. where medicines are used following marketing authorisation in the general patient population.

The use of robust pre-marketing authorisation testing and clinical trials data are vital to ensure medicines brought to market are safe, effective and are of high quality. In addition, the use of real-world evidence and real-world data is crucial to ensuring the safety and efficacy of medicines in the post-authorisation phase where patients take medicines in real-world conditions. By reporting suspected ADRs and MEs (in particular for new medicines subject to additional monitoring ▼), pharmacists help provide data on ADRs or MEs which may not have occurred as frequently (or at all) during 'ideal' pre-marketing test conditions.

For example, in paediatric or geriatric groups, in pregnancy, in poly-medicated patients with several co-morbidities (not necessarily tested in pre-marketing clinical trials) or for patients with specific genetic polymorphisms, lifestyles or health behaviours significantly different to those of the average clinical trial subject. As such, mitigation and reporting of ADRs and MEs by community pharmacists improves the evidence-base on the safety and efficacy of newly launched medicines, thereby leading to improvements in the regulatory processes, as well as in practice.

Adherence

In addition to the aforementioned reviews provided during the dispensing process, pharmacists in 13 European countries also provide targeted medication reviews as part of a semi-structured interview with their patients. These reviews focus primarily on issues related to adherence and are a unique opportunity to prevent, identify, report and mitigate suspected ADRs, MEs or other unwanted effects of the patients' medicines^{21, 22}.

21 PGEU Annual Report 2016 <http://pgeu.eu/en/>

22 Type II. http://www.pcne.org/upload/files/149_Position_Paper_on_PCNE_Medication_Review_final.pdf



Medication Reviews

A medication review²³ (MR) is a structured evaluation of a patient's medicines with the aim of optimising medication use and improving health outcomes. This entails detecting drug related problems and recommending interventions. Type 1 MRs are performed in all European pharmacies, type 2 in 13 European countries and type 3 in three European countries to date. Studies supporting the effectiveness of such interventions are increasingly being published^{24, 25, 26, 27}.

Characterisation		Information available		
Type	Level	Medication history	Patient interview	Clinical data
Type 1	Simple	+	-	-
Type 2(a)	Intermediate	+	+	-
Type 2(b)		+	-	+
Type 3	Advanced	+	+	+

Therefore, community pharmacists can play a key role in preventing, mitigating and reporting ADRs via delivery of such services. This service, provided by pharmacists in eleven EU countries, is initially focused on specific conditions or medications / classes such as those receiving medication for cardiovascular disease, diabetes, hypertension, asthma and anticoagulation or antiplatelet therapy.

Patients are recruited at the point of dispensing, counselled on relevant points about the medication and provide consent for the service. Within several weeks, a consultation between the pharmacist and patient takes place where the pharmacist conducts a semi-structured interview to identify any problems, ADRs, concerns or non-adherence to the new medication. At this point, referral can be made to the patient's doctor, if required, or appropriate advice is provided by the pharmacist and a date arranged for a final consultation within the next few weeks.

These consultations are also an opportunity for the pharmacist to provide dietary and healthy lifestyle advice to the patient. In the case of the NMS in England, it has been to be proven cost effective and to improve adherence by 10%; further study results are expected shortly^{28, 29}.

New Medicine Service

Increasingly, community pharmacies (11 countries in Europe to date) are delivering services for patients starting a new medicine which provide tailored support during the first few months of treatment²⁸. Evidence suggests that the first weeks/months of treatment are the most likely time where the patient intentionally stops taking a medication as prescribed for a number of reasons, including suffering a suspected ADR^{29,30}.

23 http://www.pcne.org/upload/files/149_Position_Paper_on_PCNE_Medication_Review_final.pdf

24 Manfrin A, Tinelli M, Thomas T, Krska J. A cluster randomised control trial to evaluate the effectiveness and cost-effectiveness of the Italian medicines use review (I-MUR) for asthma patients. *BMC Health Services Research*. 2017;17:300. doi:10.1186/s12913-017-2245-9.

25 Clyne, W., & McLachlan, S. (2015). A mixed-methods study of the implementation of medication adherence policy solutions: how do European countries compare? *Patient Preference and Adherence*, 9, 1505–1515. <http://doi.org/10.2147/PPA.S85408>

26 Jódar-Sánchez, F. et al. Cost-Utility Analysis of A Medication Review With Follow-Up for Older People With Polypharmacy in Community Pharmacies in Spain: Consigue Program. *Value in Health*, Volume 17, Issue 7, A511 - A512

27 Sorensen, L., Stokes, J. A., Purdie, D. M., Woodward, M., Elliott, R., & Roberts, M. S. (2004). Medication reviews in the community: results of a randomized, controlled effectiveness trial. *British Journal of Clinical Pharmacology*, 58(6), 648–664. <http://doi.org/10.1111/j.1365-2125.2004.02220.x>

28 Elliott, Rachel & J. Boyd, Matthew & Salema, Nde-Eshimuni & Davies, James & Barber, Nicholas & Mehta, Rajnikant & Tanajewski, Lukasz & Waring, Justin & Latif, Asam & Gkountouras, Georgios & Avery, A.J. & Chuter, Antony & Craig, Chris. (2016). Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service. *Pharmacoeconomics*. 2017 Aug 3. doi: 10.1007/s40273-017-0554-9

29 E. Mehuys, L. Van Bortel, L. De Bolle, I. Van Tongelen, L. Annemans, J. P. Remon, G. Brusselle. Effectiveness of pharmacist intervention for asthma control improvement. *European Respiratory Journal* Apr 2008, 31 (4) 790-799; DOI: 10.1183/09031936.00112007



Interactions

Medicine-medicine

Pharmacists all across Europe review medications their patients are taking as part of the dispensing process by checking the medication, dose, strength and form are suitable for each individual patient³⁰. Pharmacies maintain secure and confidential medication records of medicines taken by their patients and thus are also able to check for clinically relevant potential interactions between existing medications (prescription, non-prescription, herbal etc) as well as check for potential allergies or intolerances (such as for foods, specific medicines or excipients).

In Europe, 100% of community pharmacies are computerised and connected to the internet and the profession has significantly invested in modern information communication technologies (ICT), including pharmacy dispensing software. Such software is often integrated with clinical alert mechanisms which highlight pharmacists to potential medication interactions (or special precautions to be taken) when each medication is added to a patient's record and dispensed.

The example below shows such a clinical alert mechanism at the point of dispensing, alerting to the potential serious interaction between moxonidine (to lower blood pressure) and amitriptyline (antidepressant also used to block pain), whereby the effect of amitriptyline reduces the blood pressure lowering effect of the moxonidine thus potentially causing higher blood pressure than intended.

The screenshot displays a pharmacy dispensing software interface. A central window titled "Prescription Interaction" is overlaid on the main application. The alert text reads: "There is a possible serious interaction between Moxonidine 200mcg tabs and Amitriptyline 25mg tabs .antagonism of hypotensive effect Manufacturer advises avoid concomitant use.(Not taken together) This is regarded as a POSSIBLE MAJOR OR SERIOUS INTERACTION". The background interface shows a list of medications, including "28 Moxonidine 200mcg tabs" and "28 Amitriptyline 25mg tabs". The interface also includes various menu options and a toolbar at the bottom.

30 Type I. http://www.pcne.org/upload/files/149_Position_Paper_on_PCNE_Medication_Review_final.pdf



Herbal Medicines

Herbal medicines are often overlooked as a potential cause of an ADR, interaction or treatment failure when taken either alone or concomitantly with prescription or non-prescription medicines. As they are natural products, depending on the location, environment, cultivation and preparation conditions different batches of herbal medicines may have different potencies.

Additionally, some herbal medicines, (such as for example St John's Wort), have significant potential to cause interactions with commonly prescribed and non-prescription medicines. As such, the associated risk of ADRs or other unwanted effects is increased (for example, reduction in effectiveness of oral contraceptives and reduction in effectiveness of antiepileptics leading to pregnancy and seizure respectively). Thus, pharmacists provide information and counselling at the point of dispensing to ensure patients are aware of the risks and how they can take steps to reduce such risks.

Food-medicine

The effectiveness of many medicines can be affected by food or drink (for example, grapefruit juice and statins, cranberry juice and warfarin, leafy-green vegetables and warfarin, antibiotics and an empty/full stomach, sudden cessation of tobacco smoking and theophylline, monoamine oxidase inhibitors and numerous food and drinks). The absorption, distribution, metabolism or excretion of the medicine (and therefore the clinical effect) can be increased or reduced by food and drink, thereby increasing the chances of an ADR or sub-clinical treatment. For example, sub-optimal absorption of a medication when taken with certain minerals, or vitaminosis A in patients taking vitamin A at the same time as a retinoid medicine such as isotretinoin. As such, community pharmacists highlight the risks of such effects when dispensing medicines or supplying food supplements to their patients in order to avoid the risks of ADRs or undertreatment.

Alcohol-medicine

Several medications interact with alcohol which can cause severe ADRs and other unwanted effects (such as metronidazole and alcohol, tinidazole and alcohol, alcohol and medicines which cause sedation or respiratory depression, etc).

Therefore, community pharmacists provide information on the risks of such effects at the point of dispensing to avoid ADRs or treatment failure. Short-term use of alcohol can inhibit hepatic (liver) enzyme metabolism and long-term use can induce it, thus pharmacists also play a role in highlighting lifestyle factors which could affect medication metabolism and therefore the risk of ADRs or treatment failure.

Environment-medicine

Several medicines, particularly those used for dermatological conditions, can cause severe ADRs when unprotected skin or mucous membranes are exposed to strong sunlight (for example isotretinoin, other retinoids, doxycycline). The latter is particularly relevant as doxycycline is often used as an antimalarial and thus the patient is potentially going on holiday, perhaps to a sunnier climate. Thus, pharmacists provide counselling and information on how to avoid such ADRs such as using sun-block, lip-balm, wearing long-sleeved clothing and avoiding day-light exposure when the sun is at its strongest.

All medications can be affected by light, heat and humidity; however, some are particularly vulnerable to extremes of the environment (for example, glyceryl trinitrate and sunlight, sodium valproate and moisture). As such, pharmacists provide appropriate counselling at the point of dispensing to ensure the patient understands the precautions which need to be taken to ensure the quality of the medication is preserved (e.g. store the medicine in a cool, dry, dark place, in its original light or moisture-proof packaging, etc).

Metabolism

The degree of hepatic and renal (kidney) metabolism of medicines varies depending on the medication, the formulation and a number of other factors including the patient age and organ function.

Numerous non-prescription medications can cause potentially serious ADRs when taken with prescription medications, for example non-steroidal anti-inflammatories with anticoagulants, decongestants with monoamine oxidase inhibitors and domperidone with medicines which prolong the Q-T interval (affecting the electrical activity of the heart).



Choice of medication, form, dose and duration should be carefully adjusted to each patients' circumstances and as the experts in medicines, pharmacists ensure the appropriate medication is prescribed or recommended. For example, securely accessing renal function test results (or other relevant tests) to ensure the most appropriate medication (and dose) is prescribed or supplied could aid such safety measures.

Duplication

Despite advances in the interoperability of eHealth systems, duplication of therapy may still occur where a patient receives a prescription for the same medication, or a medication in the same class of medication, or purchases the same or similar non-prescription medication. For example, a patient prescribed co-codamol (a pain-killer containing paracetamol) purchasing a non-prescription cold and 'flu remedy containing paracetamol. Such duplications have the potential over-dose and therefore an ADR or ME.

Duplication is particularly relevant in the context of antimicrobial therapy, as, once one class of antimicrobial has been prescribed (and has failed to cure), a different class with a different mechanism of action or effectiveness on resistant microbes should be prescribed; however, this is often not the case. For example, failure of eradication of *H. pylori* with a combination of amoxicillin, clarithromycin and lansoprazole should not be followed with a second repeat course of the same combination, but instead a combination of amoxicillin, lansoprazole and either metronidazole, a quinolone or a tetracycline³¹. As such, pharmacists' knowledge of their patients, the pharmacy managed Patient Medication Records (PMRs) and Dossiers Pharmaceutiques (DPs) (Pharmaceutical Records), in conjunction with

Summary Care Records³² (SCRs) and similarly interoperable shared eHRs have significant potential to reduce ADRs, MEs, antimicrobial resistance and treatment failure in the context of duplication of therapy.

Special Patient Populations

Pregnant and Lactating Patients

As clinical trials generally do not involve pregnant or lactating women, often little is known about the potential teratogenic or harmful effects of medicines on both the unborn foetus or breast-feeding infants. As the experts in medicines, and with access to specialist resources concerning the use of medicines in pregnancy and lactation, pharmacists are well positioned to provide advice on the use of herbal medicines, non-prescription medicines, prescription medicines and healthy/harmful behaviours during pregnancy and lactation, based upon the most up-to-date and evidence-based information.

Pharmacists also play a role in advising on the appropriate consumption of foodstuffs, vitamins, minerals and other nutritional supplements to be avoided or recommended during pregnancy and lactation (for example folic acid, vitamin D).

Additionally, community pharmacists support the implementation of and adherence to RMMs/aRMMs (e.g. the pregnancy prevention programmes (PPPs)) for potent teratogenic medicines such as retinoids and valproate-related substances. Two case studies concerning how PPPs work in practice can be found in below.

31 Illustrative example only. <http://www.mims.co.uk/combination-regimens-eradication-h-pylori-nice-guideline/gi-tract/article/882106>

32 A securely accessed summary of the patients medical record including medications, known allergies and suspected ADRs

The example below, the Irish Pharmacy Union published a review article in their 'clinical tips' section of their monthly professional journal providing information on the recent EMA review of valproate-containing medicines and advice for pharmacists in practice to mitigate the risks in pregnancy.

CLINICAL TIPS

Valproate Risk in Pregnancy

In May of this year, Sanofi sent a letter to all pharmacies entitled 'Medicines containing valproate: risk of abnormal pregnancy outcomes (Epilem oral range, Epilim Chrono and Epilim IV range)'.

Included with this letter were 25 patient cards, along with a request for pharmacists to provide a patient card whenever you dispense a medicine containing valproate to a girl or woman of child-bearing age. This was in response to a Europe-wide review of the use of valproate in pregnancy and the subsequent publication of educational materials on this issue.

Europe-wide Review of Valproate-containing Medicines 2014

In December 2014, a HPA Drug Safety Newsletter included an update called 'Valproate-containing medicines: Recommendation to further restrict the use of valproate to women and girls'. A recent Europe-wide review of valproate-containing medicines had recommended strengthening of restrictions for their use and further

characterising the risk of birth defects and developmental disorders in the product information.

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).
- Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Valproate must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- All female patients should be informed of and understand:
 - The risks associated with valproate in pregnancy;
 - The need to use effective contraception;
 - The need for regular review and treatment; and
 - The need to rapidly consult if a woman is planning a pregnancy or becomes pregnant.

Further information on the Safety Concern and the Recommendations

At the same time, Sanofi sent a letter to healthcare professionals with the following additional information:

Risk of abnormal pregnancy outcomes

- Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines.
- Studies in preschool children exposed in utero to valproate show that up to 50-60% experience delays in their early development such as talking and/or walking, have low intellectual abilities, poor language skills and memory problems.
- The risk of congenital malformations is approximately 10%, for the general population, the risk is equal to above 2-3%.
- The most common types of malformations include

neural tube defects, facial dysmorphism, cleft lip and palate, craniofacial, cardiac, renal and urogenital defects, limb defects and multiple anomalies involving various body systems.

- IQ measured in a study of six-year-old children with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other anti-epileptics.
- Children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.
- Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Treatment during pregnancy

If a woman with epilepsy or bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments. If valproate treatment is continued during the pregnancy:

28 SEPTEMBER 2016

33

Additionally, in Poland pharmacists are prompted by integrated software to add pictogram stickers to medication labels and boxes for a number of safety alerts, including for pregnancy and breast feeding.



"Do not use whilst pregnant"



"Do not breast feed whilst taking this medicine"



Driving and Operating Heavy Machinery

Beyond promoting the safe, rational and effective use of medicines, pharmacists are also actively involved in the promotion of healthy lifestyles, health protection and the consideration of occupational health issues during treatment. Many medicines have the potential to cause drowsiness, blurred vision, dizziness, nausea, syncope, tiredness and lethargy (amongst other potentially hazardous ADRs) which could affect a patient's ability to safely drive or operate heavy machinery. As such, as part of the dispensing process, pharmacists provide information and warnings to ensure patients understand the potential risks of their treatment and are informed of how they can prevent such potential ADRs from affecting their home and work life.

Paediatric and Geriatric Populations

Much like pregnant and lactating patients, children, infants and the elderly (the latter often poly-medicated with other co-morbidities) are generally not included in clinical trials and hence data concerning the appropriate dose, duration, concomitant use of other medicines and the potential effects on absorption, distribution, metabolism and excretion in such patient groups are less certain than for the indicated groups (e.g. aged between 12 and 75, of a certain minimum weight etc). Community pharmacists thus provide bespoke advice and support for such patients to ensure medicines are used appropriately, safely and effectively according to up-to-date, evidence-base specialist resources available to pharmacists.

Other Special Patient Populations

There are numerous other patient populations where extra consideration needs to be given to the appropriate dose, duration and administration of medicines, also within the context of the concomitant treatment or conditions.

For example, immunosuppressed patients, those with genetic conditions leading to altered metabolism or response to certain medicines (e.g. glucose-6-phosphate dehydrogenase deficiency and treatment with several antimicrobial medications) and those with specific diseases or syndromes which contra-indicate the use of specific medicines (e.g. aspirin with those at risk from Reye's Syndrome, NSAIDs in haemophiliacs etc.). Therefore, it is crucial that community pharmacists have access to the patients medications, previous suspected ADRs, allergies, sensitivities and relevant conditions which could be affected by prescription or non-prescription medicines.

In the examples below, the French Chamber of Pharmacists produced campaign materials (posters and a video) highlighting the risks and precautions for driving whilst taking medicines.



34



34 <http://www.cespharm.fr/fr/Prevention-sante/Actualites/2017/Medicaments-et-conduite-de-vehicules-sensibilisez-le-public>



Reclassification of Medicines

Community pharmacists across Europe are engaged with MAHs and national competent authorities in the reclassification process of prescription medicines to non-prescription medicines. PGEU supports the safe, effective and rational supply of non-prescription medicines via pharmacies following consultation with a pharmacist in order to widen the access of medicines and care to the general public.

Additionally, European community pharmacists have contributed to the EU-wide reclassification of several medicines via the EMA's centralised procedure by collaborating at EU level on topics concerning RMPs and the educational materials designed for pharmacists about to supply newly reclassified medicines. These include the weight-loss medication orlistat, several proton-pump inhibitors (for gastric reflux) and the emergency contraceptive ulipristal. In fact, PGEU members recently collaborated with the MAH of the latter medication to ensure that the educational materials available for pharmacists prior to and just after launch were fit for use in practice. Thus, meaningful collaboration and consultation is required from MAHs and medicines regulators to ensure safe and successful reclassifications in practice.

Quality Control, Restrictions, Recalls and Withdrawals

Quality Control

Pharmacists adhere to Good Pharmacy Practices (GPPs), protocols and Standard Operating Procedures (SOPs) as part of their daily practice to ensure high quality delivery of pharmaceutical services. Consequently, like for CE/CPD, there is scope for integration of elements of pharmacovigilance and risk minimisation practices into GPPs, protocols and SOPs.

In the example below, the UK National Pharmacy Association published an 'Insulin identification checker' tool for use at the point of dispensing in order to facilitate the correct dispensing of insulin given the wide variety of insulins (short-acting, long-acting, pen-device, cartridges, vials etc) as well as a number of branded and biosimilar versions now on the market.

Insulin identification checker

Introduction

This resource has been created to assist pharmacists and their relevant members of staff, for example an accuracy checking technician (ACT), with selecting the correct insulin for dispensing against generic prescriptions.

When dispensing generic prescriptions, patient familiarity with a particular item should be established as the patient may be trained to use a certain type of device; for example the self injection technique associated with Lantus® SoloStar® as opposed to the Abasaglar® solution for injection in a pre-filled pen.

Table Headings

The table headings below have been selected based on the listings on the NHS [Dictionary of Medicines and Devices Browser](#) (dm+d).

- The unique code for each drug/device created by dm+d is the same as that used by prescribing and pharmacy systems when identifying products – this ensures compatibility between the systems. This is particularly important due to an increase in electronic prescribing.
- Should your pharmacy system display an error message when dispensing an electronic prescription, or when the product prescribed cannot be identified, the system supplier helpdesk should be contacted to report this. This occurs where the particular drug/device is not mapped with the dm + d code on the pharmacy system.

The four tables contained in this resource list the brands and types of insulin available for generic drug(s) commonly found:

- Table 1: Rapid acting insulin
- Table 2: Intermediate acting insulin
- Table 3: Long acting insulin
- Table 4: Mixed insulin preparations

© The National Pharmacy Association. July 2017. Produced by the Pharmacy team.
Direct Dial: 01727 891 800 Email: pharmacyservices@npa.co.uk Online: www.npa.co.uk





In addition to their expert knowledge of the use of medicines in practice, pharmacists also ensure medicines are safely procured, stored, transported and delivered to their patients under strict quality control conditions. The highly regulated environment of the community pharmacy network across Europe ensures a high quality, safe and robust supply chain of medicines and will be further enhanced with the introduction of the 'safety features'³⁶ mandated by the implementation of the Falsified Medicines Directive (FMD) in 2019³⁷ (anti-tampering devices on packages and verification of the authenticity of each package at point of dispensing).

Restrictions, Recalls and Withdrawals

Restrictions, where changes are made to the authorised or recommended use (e.g. patient group, conditions, see example above for Motilium®), are introduced following a re-assessment of the risk-benefit balance as part of a review of the safety data collected from suspected ADR reports or clinical studies.

In the example below the Irish Pharmacy Union published a supply protocol for non-prescription domperidone (Motilium®, a recently restricted medicine) to facilitate the safe supply in community pharmacies.

38

IPU Domperidone Sales Protocol

Background

In April 2014, the European Medicines Agency (EMA) issued new recommendations to restrict the use of domperidone-containing medicines over concerns about the medicine's effects on the heart. The recommendations were originally made by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) after a careful evaluation of the benefits and risks of such medicines. PRAC found that people taking domperidone may have an increased risk of serious cardiac adverse drug reactions. A higher risk was observed in patients over 60 years old, adults taking daily oral doses of more than 30mg and those concomitantly taking QT-prolonging medicines or CYP3A4 inhibitors.

In light of the EMA review, a number of EU countries, including the UK, have re-classified all domperidone-containing products to prescription-only. However, the HPRA has decided to continue to allow domperidone to be supplied without prescription in Ireland subject to a number of conditions. Consequently, it is vital that pharmacists follow the recommendations in this protocol.

To facilitate a more professional approach to a consultation for the supply of domperidone, we have produced a module on www.ipunet.ie which will assist pharmacists in the decision to supply domperidone. We highly recommend that all pharmacists use this IPU NET module.

This sales protocol should be read in conjunction with the PSI Guidance on the Safe Supply of Non-Prescription Medicinal Products Containing Domperidone Oct 2014 and the Summary of Product Characteristics (SPC) for each domperidone-containing medicine. There are currently three authorised non-prescription products containing domperidone listed on the IPU Product File: Motilium 10mg Tablets; Motilium Fastmelts 10mg Tablets; and Domerid Relief 10mg Tablets.

38 https://ipu.ie/ipu_categories/domperidone-2/

36 Anti-tampering measures and verification of a medicine's authenticity at point of dispensing

37 Article 54a (2), (d) Directive 2011/62/EU



Recalls, to varying degrees of severity (and therefore varying levels of urgency) occur as a result of the quality, safety or authenticity of a medicine being brought into question. An issue in the manufacturing, processing, packaging or distribution of the medicine may trigger a recall of specific batches of medicines, for example, bacterial contamination during manufacturing or incorrect labelling or packaging.

Withdrawals occur as a result of either a decision by an MAH to no longer market the medicine, or more commonly, following a decision by either a national competent authority or the EMA after a re-assessment of the risk-benefit balance. As previously explained above, such withdrawals (e.g. Vioxx®, Mediator®) occur following a review of the safety data collected from suspected ADR reports or clinical studies where benefits are no longer thought to outweigh risks.

Pharmacists are often the last HCP to have contact with the medicine before supply to the patient and thus play a vital role in preventing the supply of recalled or withdrawn medicines and ensuring restricted medicines are supplied in accordance with new regulations.

Should there be any reason to recall or withdraw medicines, pharmacies react rapidly to segregate affected stock for return to the wholesaler from the pharmacy for destruction and in some cases, from the patients when necessary. With the increasing distribution of biological and biosimilar medicines via primary care (and hence community pharmacies), pharmacists have an opportunity to capture and record the batch numbers / lot codes and other pertinent information relevant to recalls or safety alerts for this growing and complex group of medicines. For restrictions, pharmacists often receive communications from MAHs, national competent authorities and the EMA, but also participate in regular CPD activities to update their knowledge on recent restrictions.

electronic Health Records (eHRs)

Pharmacists can also disseminate safety alerts concerning medicines rapidly to patients and the public, particularly when aided by modern ICT.

In the examples below, dedicated websites are available to provide up-to-date information and educational materials on medicines subject to additional monitoring, developed in collaboration with the French Chamber of Pharmacists.

39

40

39 <http://www.cespharm.fr/fr/Prevention-sante/Actualites/2017/Valproate-et-derives-une-indispensable-carte-educationnelle>

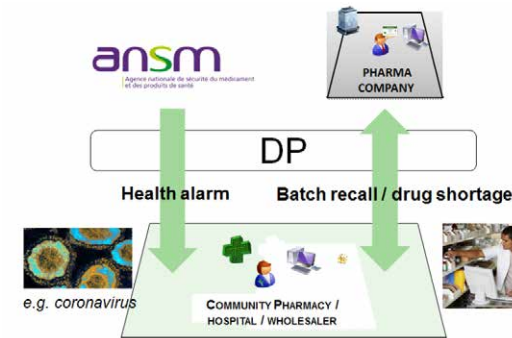
40 <http://www.meddispar.fr/Actualites/2017/Valproate-et-derives-nouveau-pictogramme-de-renforcement-de-l-information-sur-les-risques>



As mentioned previously, pharmacists in Europe keep confidential and secure records of medicines dispensed to their patients in order to facilitate the safe dispensing of medicines and information. These electronic medication records (also known as patient medication records – PMRs) are evolving in a dynamic eHealth environment with advances in interoperability with ePrescribing systems.

'Dossier Pharmaceutiques' (DPs) are pharmaceutical records (records of recent prescription and non-prescription medicines) managed by pharmacies which, with appropriate patient consent and justified clinical need on the part of the pharmacist, and shared between pharmacies in Belgium and France and have the potential to be shared with other HCPs such as hospital and primary care physicians. This system reduces duplication, abuse, errors, interactions, ADRs and MEs. Additionally, an alert system is incorporated into DPs to ensure medicines subject to recall or subject to additional safety measures can be effectively and systematically communicated.

In France, patients have a "Dossier Pharmaceutique"^{41, 42} maintained by community pharmacists following the establishment of the legal framework in 2007, which delegates responsibility for the service to the French Chamber of Pharmacists. This service displays all treatments, (prescription or non-prescription), dispensed to a patient during the previous four months (biological medicines for the past three years and vaccinations for the past 21 years) regardless of the pharmacy in which they were delivered. To date, almost all French pharmacies have implemented this service accounting for more than 330 million instances of sharing patient data, including over 100 'alarm bells' and medication recalls.



Community pharmacists have 'read and write' access to the Dossier Pharmaceutique and will shortly be joined by all hospital physicians who will receive read-access following a successful pilot. Half of the population in France has a Dossier Pharmaceutique with 80.000 new Dossiers being created each week. The linkage between secondary and primary care of this service has facilitated clinical interventions by pharmacists and avoided medication related problems. Two studies⁴³ found that the Dossier Pharmaceutique helped pharmacists detect medication interactions and contraindications, often in cases of commonly-used, non-prescription medicines.

41 <http://www.ordre.pharmacien.fr/Le-Dossier-Pharmaceutique/Qu-est-ce-que-le-DP>

42 https://www.medetel.eu/download/2016/parallel_sessions/presentation/day2/Olivier_Por_Overview.pdf

43 <http://www.ordre.pharmacien.fr/Communications/Communiqués-de-presse/Evaluation-du-DP-de-sa-mise-en-oeuvre-Interventions-Pharmaceutiques>



Belgian pharmacists maintain a confidential medication record for their patients. The Belgian “Dossier Pharmaceutique” contains details on dispensed medication (prescription and non-prescription) and is used to prevent medication and disease-related problems such as detecting interactions, medication abuse, ADRs duplication of therapy and of course to monitor adherence. This service is led by the Belgian professional associations for pharmacists in order to facilitate improved patient safety and provision of pharmaceutical care.

Trc	Stat	Geschieding	Begin	Einde
GFD 1		ASPIRINE 100 MG COMP 30	02/14	02/14
GFD 1		ASPIRINE 100 MG COMP 30	02/14	02/14
GFD 1		ASPIRINE 100 MG COMP 30	02/14	02/14
GFD 1		NUROFEN 30 TABL 200 MG	02/14	02/14
GFD 1		NUROFEN 30 TABL 200 MG	02/14	02/14
P 19		ASPIRINE 100 MG COMP 30	02/10	02/14
P 19		ASPIRINE 100 MG COMP 30	12/10	02/14
GFD 1		NONABRITINE CAPS 16X 500MG	02/14	02/14
GFD 1		CLONIDYL CAPS 16X 500 MG	02/14	02/14
GFD 1		NUROFEN 30 TABL 200 MG	02/14	02/14
P 4		DAFALGAN FORTE DROOG 15 TABL 90	02/14	02/14
GFD 1		NUROFEN 30 TABL 200 MG	01/14	01/14
GFD 1		CLONIDYL CAPS 16X 500 MG	01/14	01/14
GFD 1		CLONIDYL CAPS 16X 500 MG	01/14	01/14
P 3		ALTERNA POST OP LEDIGB. HUSTER 10,70MM 6 12000	01/14	01/14
P 4		ALTERNA FREE GIZ TRANSP MAAS 20,70MM 30 46326	01/14	01/14
P 3		COMBIPLAST SUPERFLEX PL BG 35,42NM 5 FF3957	01/14	01/14
GFD 1		CLONIDYL CAPS 16X 500 MG	01/14	01/14
P 16		FILATINE COMP 20X 10 MG	01/13	01/14

These records are capable of being shared (subject to patient consent and privacy protocols) with all participating Belgian pharmacies through the “Dossier Pharmaceutique Partagé”⁴⁴ or DPP. This increases patient safety when dispensing medication and making available relevant, accurate and high-quality information on a patient’s medication history. The system is fully integrated to existing pharmacy dispensing software.

44 https://www.medetel.eu/download/2016/parallel_sessions/presentation/day2/A_shared_pharmaceutical_record_in_a_Belgian.pdf

Summary Care Records

Similarly to DPs, ‘Summary Care Records’ (SCRs) are summarised records of relevant patient information (medications, known allergies and ADRs) in the UK are formed from the patient’s general practitioner record which can easily be shared with other HCPs where patient consent and justified clinical need are present.

Pharmacy access to SCRs is seen as a first step to ‘read and write’ access to the full eHR in the UK. A proof of concept report in England²⁶ showed that in 92% of encounters where the SCR was accessed, the pharmacist avoided the need to signpost the patient to another health service. In 18% of encounters where the SCR was accessed, the risk of a prescribing error was avoided. 92% of pharmacists agree or strongly agree that using the SCR improved the service they provide to patients. Explicit patient consent is required and there is strict control of access to records. Pharmacies must appoint a ‘Privacy Officer’ to manage the governance of SCRs.

Abuse

In a similar context to the issue of duplication, pharmacists’ knowledge of their patients and access to PMRs, DPs and SCRs have the potential to detect, reduce and avoid potential misuse and abuse of both prescription and non-prescription medications. For example, frequent dispensation or supply of opioids, laxatives, decongestants or topical steroids etc.

Off-label Use

Medicines in Europe are authorised with specific indications, doses, routes of administration or patient groups as described in the SmPC. Use of the medicine outside of these conditions is termed ‘off-label’⁴⁵. Whilst HCPs should ensure medicines are used within the terms of their marketing authorisation, often the needs of the patient outweigh this, for example, for use in paediatric or geriatric populations. Particular attention should be given to suspected ADRs and MEs arising from medicine used off-label. As such, pharmacists should have access to the indication of each medicine (e.g. stated on the prescription or via interoperable shared eHRs) to allow pharmacists to provide appropriate information to patients and take action to report ADRs or MEs should they occur whilst medicines are used off-label.

45 <http://www.braincouncil.eu/golup/wp-content/uploads/2015/05/GOLUP-declaration.pdf>



PGEU's Work on Pharmacovigilance

EMA's Healthcare Professionals' Working Party (HCP/WP)

Representation

The PGEU is a proud member of the EMA's HCP/WP, a network of European healthcare professionals associations' stakeholder groups. The HCP/WP acts as platform for exchange of information and discussion of issues of common interest between HCPs and the EMA. Formed in 2013, it builds on the previous established relations between HCPs and the EMA. The WP provides recommendations to the EMA and its human scientific committees (such as PRAC) on issues related to medicines. The HCP/WP meets three times a year at the Agency's Headquarters, along with the Patients and Consumers Working Party. Membership of the HCP/WP provides an excellent opportunity for the needs, perspectives and experiences of community pharmacists to be reflected in the work of the EMA and related policy, communications and guidance.

Additionally, between 2015-2017 PGEU was the co-chair of the HCP/WP's Topic Group (TG) on Risk Minimisation Measures (RMMs) - see below for more details.



46

46 http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000735.jsp&mid=WC0b01ac05809e2d8e

Consultations

In the past three years, PGEU has responded to over 50 public and targeted consultations for the EMA as part of its role in the HCP/WP. The responses comprised general PGEU feedback, as well as individually and in smaller groups, as several PGEU member representatives are approved as technical experts for the EMA. The majority of consultations for which PGEU provided input were related to pharmacovigilance, medication safety and related issues.

Participation in EMA Workshops

In the past three years, PGEU has presented, participated in panel discussions or actively contributed to over 30 workshops and meetings hosted by the EMA on various topics, most notably on pharmacovigilance, medication safety and related topics. PGEU is often invited to present or contribute to EMA workshops as a result of PGEU's active contribution to pharmacovigilance activities and being the representative organisation of the 400.000 community pharmacists in Europe. Examples include workshops on measuring the impact of pharmacovigilance activities, medication errors, medication or class-specific workshop consultations and the annual Pharmacovigilance Stakeholders Forum.

Public Hearings

One of the developments following the 2012 EU pharmacovigilance legislation was the introduction of 'Public Hearings' as part of PRAC's work. Public hearings are organised in order to give EU citizens a voice in medication safety evaluations and enable them to express their views on issues related to the safety of specific medicines and the management of such risks.



The first public hearing is due to be held under the auspices of the September 2017 PRAC meeting and will focus on sodium valproate (and related substances) in the context of the recent PRAC referral on this medication. As valproate is a commonly dispensed medication in community pharmacies, this referral and public hearing have particular relevance to community pharmacists across Europe and PGEU has been closely following the work concerning the valproate referral and public hearing.

EMA Pharmacovigilance Risk Assessment Committee (PRAC)

Since PRAC's formal inception in 2012, PGEU has played a pivotal role in PRAC by having a PGEU member representative nominated by the European Commission as the official representative for HCPs on the committee. A PGEU member representative held this position for the first mandate and PGEU continues to have a member representative nominated for the second mandate. PGEU's presence on PRAC provides the opportunity to bring a practicing healthcare professional's perspective to the work of PRAC more generally, but also the perspective, experiences and opinions of pharmacists to relevant discussions in the committee.

This is particularly important when the practical aspects of medicine prescribing, supply issues and their associated risks are being discussed by the committee. Input from a HCP/pharmacist can facilitate the PRAC in discussions when assessing changes to a medicines licence. It can also help in assessing the need to communicate directly with healthcare professionals, how this should be done and the value of doing so.

EMA HCP/WP Topic Group on Risk Minimisation Measures

As part of PGEU's role in the HCP/WP, between 2015-2017 PGEU was the co-chair of the HCP/WP's Topic Group (TG) on Risk Minimisation Measures (RMMs). As a result of the work conducted in the RMM TG, several recommendations⁴⁷ were made to the EMA and PRAC for consideration to improve the implementation and adherence to RMMs. They include a recommendation to involve HCPs earlier on in the development process of additional risk minimisation measures and likewise to involve HCPs earlier on in the development of routine risk minimisation measures.

Additionally, the TG recommended that guides and checklists should cover all HCPs involved in medication use, including pharmacists and that information provided to patients could be better balanced / articulated (e.g. include side effect frequencies, information on risk of other medicines in same class / alternatives). The TG also recommended that consideration should be given to making information available on the outside of the package and in the SmPC, as a summary, prompt or removable card to facilitate dialogue with patients.

The TG made further recommendations that communications should be targeted to the various audiences with appropriate tools, using mixed media channels and the use of scientific publications, communications or events for disseminating information concerning RMMs.

The TG also proposed points for consideration by HCPs, including the possibility of incorporating RMMs into institutional protocols or guidelines and incorporating RMMs into HCP CE/CPD. Furthermore, the TG recommended widening access to shared eHealth records (with indications / diagnoses / reported ADRs or side effects) and encouraging multi-professional collaboration and shared responsibilities. Finally, reflection on dissemination practices concerning RMMs for European level stakeholder / representative bodies could also be considered.

47 See Annex 5



4. Conclusions and Recommendations

Conclusions

This paper, timed with the fifth anniversary of the 2012 revisions to the EU pharmacovigilance legislation, shows the continued need to involve community pharmacists in the EU pharmacovigilance system, in particular, in supporting pharmacists' expanding and evolving role to support patient and medication safety. This paper shows how community pharmacists are engaged in pharmacovigilance activities through their education, training, continuous professional development; their expert knowledge of medicines and ability to improve adherence and the safe, effective and rational use of medicines; their accessibility and embracing of innovative technologies; their responses to restrictions and other safety measures in practice; and their engagement in both national and European initiatives.

However, further support is needed from health policy makers and health systems payers in order to maximise the potential benefits community pharmacists can make to strengthening and improving the EU pharmacovigilance system and patient safety.

Recommendations

As a consequence, the PGEU makes several recommendations in order to maximise the potential contribution community pharmacists can make to pharmacovigilance and risk minimisation activities. They are as follows:

1. Patient-facing pharmacy services that support the safe, effective and rational use of medicines are beneficial in minimising risk (e.g. medication review and new medicine services) and should be expanded and supported by policy makers and health systems payers;
2. Where feasible, pharmacists should have access to shared electronic health records to ensure continuity of care and reduce the risks of adverse drug reactions, medication errors, interactions and other harmful events;
3. Indications should be communicated to pharmacists (e.g. on the prescription) to ensure the most effective and appropriate therapy and counseling is provided, as well as to ensure the correct reporting of suspected adverse events from the use of medicines off-label;
4. Further interdisciplinary collaboration is welcomed between pharmacists and other healthcare professionals to maximise the benefits for patient safety (e.g. more effective problem solving and prevention of adverse events in partnership, continuity of care, reduced costs and administrative burden);
5. Continued collaboration between national pharmacy associations and national medicines agencies and the PGEU and the European Medicines Agency is welcomed to further strengthen and support the role and contribution pharmacists can make to patient and medication safety;
6. Relevant authorities and organisations are incorporating good pharmacovigilance practices, risk minimisation measures and medication safety activities into Good Pharmacy Practices, standard operating procedures, institutional protocols, continuous education, continuous professional development and pharmacy education and training. Such incorporation should be encouraged and supported.



Contacts

Rue du Luxembourg 19 | 1000 Brussels | Belgium
T +32 (0)2 238 0818 | F +32 (0)2 238 0819
Email: pharmacy@pgeu.eu



Please visit our website on www.pgeu.eu