



**Exploring the practical implications of the new
Pharmacovigilance legislation to enable
patients and health professionals to act more
effectively on adverse drug reactions**

**The Report
September, 2010**

Introduction

In the third week of September 2010, the European Parliament gave its support to the new draft

Pharmacovigilance started some forty years ago with the setting up of spontaneous reporting schemes for suspected adverse drug reactions (ADRs). Since then, along with the consolidation of such systems around Europe, important new developments have taken place, reinforcing ability to identify and characterise medicine safety issues earlier and on more scientific grounds.

Reports of suspected ADRs form the basis of the surveillance of medicines after their marketing authorisation. The World Health Organisation (WHO) describes pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse affects or any other possible medicines-related problems".

reports, summaries of product characteristics and patient information leaflets. The portals will also tell patients how to report any suspected adverse reactions.

These web portals will be linked to the EudraVigilance database – the single point of receipt for all pharmacovigilance information. The database, run by the European Medicines Agency, will be fully accessible to the Member States and the European Commission, while access "to an appropriate extent" will be available to industry, doctors, pharmacists and the public.

The Directive requires additional monitoring of certain new medicines, which will be identified by a black

legislation improving the pharmacovigilance system in the EU, making the reporting of adverse drug reactions (ADRs) easier and introducing special provisions for treatments that need additional monitoring.

The pharmacovigilance Directive, which had already been agreed by the European Parliament's Public Health Committee, was overwhelmingly endorsed by the plenary in Strasbourg.

The legislation must be put into effect within 18 months of its publication in the EU Official Journal and will see the European Union and its Member States set up pharmacovigilance websites.

The national web portals, to be linked to the EU's own, will include assessment

symbol and an explanatory sentence in the patient information leaflet.

The European Commission says that the new legislation aims to consolidate, streamline and genuinely strengthen the Community's pharmacovigilance system and, therefore, improve patient safety in Europe. Crucially, the reporting of ADRs by patients and pharmacists is given new impetus.

On 15 September 2010, on the eve of the European Parliament vote on the legislation, Linda McAvan, MEP, hosted a seminar in the Parliament. The event was jointly organised by the Pharmaceutical Group of the European Union (PGEU) and the European Patients' Forum (EPF). More than 60 delegates were in attendance, among whom were representatives from the European Commission, the European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the Standing Committee of European Doctors (CPME), and other stakeholders including patients and the pharmaceutical industry.

Opening Remarks

The discussion was opened by **Linda McAvan**, MEP, the Rapporteur on the pharmacovigilance strategy (Directive and Regulation) at the European Parliament; a key player in bringing the legislation to the recent Parliamentary vote and thus into eventual effect.



In her brief introduction Ms McAvan pointed out that, as she spoke, the deadline for final amendments was passed and she expressed a hope that none had been tabled. (In fact, it transpired that there were no further amendments).

The role of Rapporteur, she said, had been a major learning curve involving complicated technical issues but, now that the legislation was about to be put in place, her main desire was to see exactly how those in the front line – the pharmacists, other healthcare professionals and patient groups – would implement the legislation in the interests of patient safety.

Ms McAvan's brief introduction was followed by a welcome from **John Chave**, Secretary General of PGEU, who also had the task of moderating post-presentation questions, before **Anders Olauson**, the President of EPF, took the podium.

The rate of patients' deaths and harm caused by adverse events is estimated as the fifth largest cause of death in hospital – yet the rate of reporting adverse drug reactions (ADRs) is as low as 10-25% of all cases.

The new legal provisions facilitating direct patient reporting to health authorities represent the added value of spontaneous patient reports, providing crucial complementary information to those submitted by health professionals. Evidence suggests that patients tend to directly report symptoms such as sexual dysfunction, suicidal behaviour, and so on, which they may find uncomfortable to mention to health professionals.

It is believed that patient reports usually capture the personal experience of ADRs in a way that reports by the healthcare professionals cannot. Patients have a unique knowledge and experience of side effects and the adverse effects of the medication they take. This knowledge should be used for the benefit of other patients as well as health professionals.

Mr Olauson called the seminar a “*crucially important and extremely timely event*,” going on to introduce his organisation, the EPF, as the umbrella organisation for patient groups, representing the interests of more than 150 million patients across Europe. He offered thanks to Ms McAvan, describing her as “*a long-time champion on patient rights*”, as well as the PGEU for its close cooperation with EPF.

In respect of the new legislation, Mr Olauson told the audience that EPF had worked intensively with the EU institutions to ensure that it would be “*as patient-centred as possible*”, adding that he was pleased to see the degree to which EPF's views have been taken on board, with an important role for direct patient reporting (DPR). He told the attendees that he was “*very pleased*” with the inclusion of DPR in the legislation. It would lead to better safety data and patient empowerment, and thus to greater patient safety. Key to the success of DPR would be patients' health literacy, he

added, pledging that EPF would continue to work passionately on this and other patients' issues, supported by its allies in the Parliament and health professionals' organisations.



Anders Olauson

Mr Olauson concluded by telling the attendees: “*By your very presence today you are sending a really strong message about direct patient reporting*”.

A Perspective from the European Commission

The first speaker to address the audience was **Lenita Lindström**, who is a Senior Policy Officer at DG SANCO, the European Commission. She talked about ‘**The new pharmacovigilance legislation and reporting of adverse drug reactions by healthcare professionals and patients.**’

Ms Lindström explained that the pharmacovigilance legislation was part of the ‘Pharmaceutical Package’ put forward by the European Commission in 2008 and comprising three legislative proposals, the other two being on anti-counterfeiting and information on prescription medicines. She added that it was a surprise to many that the pharmacovigilance legislative proposal would be the first one to come into force.



Lenita Lindström

The reason for new legislation was that the old system had shortcomings – it was complex, and it was unclear who had what role. So the clarification of tasks – who is responsible for what, and how various stakeholders can work together – was fundamental. The preparatory work on the legislation took five years in itself.

Once the law starts to work, DPR will soon be possible in all Member States, which is not the case at the moment. However, reporting of ADRs is only one part of the legislation. There will generally be more

transparency in the system, and patients will be better involved in patient safety issues.

The role of the EMA has also been reinforced, with the creation of the new Pharmacovigilance Risk Assessment Committee (PRAC), which will include representatives from each Member State as well as representatives of healthcare professionals and patients' organisations and have a role looking at all pharmacovigilance tasks.

Ms Lindström said the EudraVigilance database will be vital to how the new set-up will work. It will collect information gathered by the portals in each individual Member State. Healthcare professionals and patients will file their reports to the competent national authority, which will then pass this on to EudraVigilance. The EMA already has the database up-and-running well, she said, although it will obviously take a little time for Member States to properly learn how it works.

One matter that has yet to be decided is how much access individual healthcare professionals and patients will have to the site, given that EU data protection laws apply. It is important, said Ms Lindström, that personal data and commercial information are protected, although the European Commission is still working to make the whole process as transparent as possible and aiming to ensure that any final conclusions and recommendations are published. This transparency will lead to better informed professionals and patients.

In conclusion, Ms Lindström expressed the hope that the legislation would lead to *"better protection of public health, which is what we all work towards"*. When asked from the floor about perceived resistance to direct patient reporting, she conceded that there had been a fear of an extra burden and possible repercussions on necessary resources. Once DPR was launched EU-wide, there would obviously be a lot of reporting at first before it stabilised, but fears had been allayed by the fact that Member States with experience of DPR regarded it as an overall beneficial experience.



Kees van Grootheest

An Academic Perspective

The second presentation came from **Kees van Grootheest**, the Director of the Netherlands Pharmacovigilance Centre

(Lareb) and Professor of Pharmacovigilance at the University of Groningen. The title for his talk was **'The Role of Pharmacists and Patients in Pharmacovigilance'**.

Prof Grootheest began by defining pharmacovigilance as a science (see box on page 2). It is not just about rules and regulations, he said, but about aiming at good care. The main method of learning and gaining information is direct reporting from patients and healthcare professionals. *"Spontaneous reports are the basis of our new knowledge,"* he said.

He described ADR reporting as an effective tool and quality indicator – the 'top of the pyramid' containing all problems associated with medicines therapy and drug-related problems.

Prof Grootheest gave a brief background on how things work in the Netherlands. He said the Dutch system tries to stay close to daily care and accepts reports from physicians and pharmacists. Additionally, since 2003, patients can report directly to the national agency, through only via the internet. This was due to early concerns that there would be too much 'noise' from reports.

Pharmacovigilance signal detection is one of the best ways to detect and prevent adverse events. The signals are detected on the basis of spontaneous reporting of ADRs. Then these cases are carefully studied and categorised into a database. A pattern is established through a scientific method of computation based on data tables. This gives a fair idea of the potential signals that lead to adverse events

And reports are increasing, he said.

However, it is not just quantity, but quality too that is increasing. He gave examples of new signals (see box on this page) identified as a result of patients being more likely to report certain issues, such as an addiction to gambling, as a side-effect of a medicine. A doctor may treat this with scepticism, but patients report because they *"want to be taken seriously and want something to be done"*.

It turns out that the patient report being a final trigger for regulatory action was equal in number to trigger-reports from pharmacists. Prof Grootheest described the patient reports as really useful and of surprisingly high quality. But, overall, we need to get information from all those involved: the 'triumvirate' of doctors, pharmacists and patients. This is where new knowledge comes from. In the Netherlands, the

system is based on getting patients and pharmacists to report on new medicines together.

“The message matters, not the sender,” was the key message from Prof Grootheest. And transparency is vital, because secrecy is counterproductive.

At the moment, Lareb is working with the WHO on implementation of guidelines in other countries on patient reporting.

A Patient’s Perspective

Third to speak was **Bartłomiej Kuchta**. Mr Kuchta is a patient and the President of the Polish Association of Patients with Spondyloarthritis.¹ His report was titled **‘The Patient’s Perspective on Spontaneous Reporting of Adverse Drug Reactions.’**

Mr Kuchta explained that patients are now more informed, have greater social awareness and work more closely with doctors. More demands for change are coming, with growing emphasis on self-management, e-health technologies and personalised healthcare. Patients’ empowerment is an essential aspect of these developments.

Mr Kuchta praised the patient-reporting part of the legislation; patients have a unique knowledge and this should be used productively. He reiterated a common theme – that sometimes patients don’t feel comfortable reporting to their doctors. They need access to reliable safety data and, he said, *“we as patients welcome being granted more access to this information”*.



Bartłomiej Kuchta

In Poland, government regulations state that the cheapest medicine available on the market is the one that must be dispensed as a first line treatment. The cheapest medicine can only be exchanged under specific conditions, including in the

case of adverse reactions. With spondyloarthritis, physicians wishing to prescribe an alternative medicine noted adverse reactions as the reason for switching. Adverse reactions were thus noted in the

¹ Ankylosing Spondylitis, known as Bekhterev’s disease, Bekhterev syndrome, and Marie-Strümpell disease

patients’ records, but not passed on to the relevant authority.

Although the physicians believed they were acting in the patients’ interest, nevertheless, if patients could have reported adverse reactions directly and had full access to safety information, Mr Kuchta said, such issues could be identified much earlier. Patients would be able to work more effectively in partnership with their doctors and the government to ensure the right medicines were made available.

As a result of a question from the floor regarding Mr Kuchta’s talk, it became very clear that all participants endorsed a ‘no blame’ principal on reporting of medication errors. A ‘no blame’ principle is vital to encourage all parties to report ADRs and break down what can sometimes be a barrier between doctor and patient.

A further point was made by Mr Chave that, following the example of the Netherlands, pharmacists and doctors need to work together much more than currently in many EU Member States.

A Regulator’s Perspective

Next on the podium was **June Raine**, Director of the Division of Vigilance Risk Management, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom. Her presentation was entitled **‘Adverse Reaction Reporting – A Regulator’s Perspective’**.



June Raine

Dr Raine opened by referring to the great sense of excitement shared by all in the room. *“But where to next?”* she asked. *“What can we all add to make the new legislation work?”* Given the seminar’s topic, Dr Raine was keen to stress that the cornerstone of pharmacovigilance is spontaneous reporting. It is very important to the regulator, notwithstanding the fact that there are many other ways of gathering data. In a recent survey, no less than 500 key signals came from patients.

“Why is DPR so important?” Dr Raine asked, reminding the gathering that it was the 50th anniversary of the thalidomide tragedy. Thalidomide

affected thousands of pregnancies before the huge problem was flagged up – and “*we could have done much better*”, she said.

But, despite the magnitude of what happened half-a-century ago, pharmacovigilance is not always about pulling medicines off the market. Gathering data is also about managing risk and allowing people to gain the benefits of sometimes life-saving medicines.

Dr Raine spoke about the UK’s experience of patient reporting for the past five years and enthused about the richness of detail. Patients know, she said, how a medicine affects their life, well-being, and ability to work. Spontaneous reporting is a vital early warning system. And it’s great value for money, she added.

But there are still questions: We can do better under the new legislation, but how do we deal with under-reporting? How do we ensure good follow-up information? How do we pick up signals and move faster? One major benefit is that we can now monitor new drugs, she added, with a majority of reports now concerning such novel products.

Dr Raine was also one of a number of people who mentioned that not everyone was happy – or able – to use the internet to report. Perhaps we can have a system of telephone reporting, say, for the elderly, was her suggestion.

Summing up, Dr Raine said that all 27 EU Member States have different stories to tell. Yet all clearly have a contribution to make, and the question is how we can capture that learning effectively. We must find a forum for exchanging this information, she said, because spontaneous reporting is a key to patient safety. The new legislation will support optimal use of this information. And the clear message is that everyone has a part to play – that every report matters.

Finally, she said that regulators need strong links with health professionals, and asked whether the latter’s reporting should be a legal obligation or, slightly softer, be considered part of professional duties. If so, how to get that message, that reports make a difference, out there?

A Perspective from the European Medicines Agency (EMA)

After June Raine came **Peter Arlett**, Head of Pharmacovigilance and Risk Reactions Management, Patient Health Protection at the European Medicines

Agency. His presentation was called ‘**EMA Working to Strengthen Patient Health Protection.**’

Mr Arlett said how fantastic it already was to have all the stakeholders present in one room. In view of the legislation and what will follow, he predicted “*a steep curve ahead*” but emphasised “*a great opportunity*”. He added that the EMA wants to enhance its work with patients, and the subject of pharmacovigilance now looks set to be top of its list in the wake of the new legislation.



Mr Arlett also gave an insight into EMA operations and philosophy, stating that the front line is the EU Member States, and EMA’s job is to bring the best aspects of healthcare together – enabling, facilitating and, supporting the Member States. The agency’s job is essentially a “*calibration*” of all stakeholders to better protect the public health.

He described what in 1995 was a young, ‘little’ agency and how it is now the hub of the European regulatory network. It is not simple, he declared, because the EMA has to work with patients, doctors, pharmacists and industry, and that’s just in Europe. But EMA is global too, working with WHO, in America and so on.

Mr Arlett emphasised that much of the scientific work for the agency is done by the Member States, and the two share resources.

Warming to his theme, Mr Arlett said that this cooperation is about pooling expertise, sharing standards, peer reviewing, better use of resources, benchmarking and comparing health systems. He also pointed out that having a bigger population to look at – through the EU Member States – helps to gather more data. “*Can you detect issues earlier using a bigger data base?*” he asked. Yes you can, was his conclusion. Also, he added, if a medicine is used in two different ways in two different countries, this might have important implications for managing risks.

There is “*no doubt*” Mr Arlett, said, “*that working together makes us stronger*”.

The EudraVigilance resource was, he revealed, “*hotly debated during the legislative process*”, but he described it as “*a fantastic resource for detecting and*

analysing adverse reactions". To date, he told the room, there have been more than 1.5 million case reports of suspected adverse reactions.

More specifically, in respect of the 'pandemic flu', he said that spontaneous reporting was the bedrock of the safety monitoring. Some people argue that the way of the future is all about electronic health records (EHR), he explained. But it's not just EHR, he countered firmly. *"This is the reality – it is about spontaneous reporting."*

Concluding, he called for continued investment in these tough economic times and said: *"We can do better, we want to do better and the legislation will help us do that. Of course, everyone should be reporting, but the challenge now is how to do it well."*

EMA, he added, welcomes the legislation *"with open arms but a little trepidation"*. This is because there is still a lot to be done.

An Industry Perspective

David J Lewis was next to speak. Dr Lewis is Global Head of Pharmacovigilance Systems & Safety Data Management and Deputy EU Pharmacovigilance Qualified Person at Novartis Pharmaceuticals UK Ltd. His presentation was entitled **'Regulatory Framework for a Positive Benefit Risk Profile of Medicines'**.

Dr Lewis said he wanted to represent himself as a patient, as well as being from industry, explaining that in the past he has filed two reports from a patient point of view – one for himself and one for his sister. His doctor was not keen to report, so he did it himself. *"It's good, it works,"* he said, adding that he was glad of the opportunity.

To open on the legislation in general, he said it underpins industry working together with the pharmacists, patients and health professionals, *"so it's really important for us"*.

He talked of looking at risk, but emphasised that we have to look at benefit as well. According to a recent report, he said, overall life-span is increasing and we live longer and longer. If we took away every risk of every medicine, it would add just another 40 minutes to this extended lifespan. But, if we took away all the benefits, it would shorten our lives by 15 years.

He explained that when ADR reports reach a company, it collates them, follows them up to get

good data, and then passes the information on to regulators where required. He emphasised that industry is evaluating – using good science – at the same time as the regulator, while formulating summaries of product characteristics and/or a patient information leaflet. *"We get the information to the right people,"* Dr Lewis said, so there is feedback and transparency from industry.



David J Lewis

Dr Lewis also explained that pharmacovigilance is about anticipating the problem, managing risk, minimising it, and dealing with it in real time. Industry has to make robust decisions based on the evidence, he added, reminding the room that *"the tools are now out there – EudraVigilance being a prime example,"* in order to measure what is the public health benefit. Spontaneous reporting was clearly vital in gaining evidence, he maintained.

From the industry point of view he felt that the new PRAC committee at the EMA is a really good idea. It spans the EU and strengthens the coordination of activities. It gives clearer roles for Member States, the EMA, and also industry. EudraVigilance is a key element, being good at getting information to where it should be evaluated, he said, adding: *"I want to go further and ask for extra access for industry and patients. This brings more transparency."*

He welcomed the additional monitoring for new products but warned that, if the EU chooses the wrong symbol or too-strong warnings, people will not take the medicine. If a warning merely emphasises the risk, rather than the benefit, patients get nervous. Also, messages of scientific content have to be meaningful. *"Perhaps we may have to 'dumb things down',"* he said.

In the end, he repeated that we all want patients to report ADRs, adding that at the moment, some



Member States do already facilitate this but some never have. “We need that harmony,” was Dr Lewis’s final message. “This is the challenge.”

He closed the meeting by saying: “Let’s work together to make this a reality!”

Closing Remarks

After Dr Lewis had finished speaking, there were closing remarks by **Filip Babylon**, the President of the PGEU.

First, he thanked Ms McAvan and her excellent team for agreeing to sponsor the event. The way that Ms MacAvan dealt with the pharmacovigilance directive, which would soon become law, had been a model of efficient and effective law-making in the interest of Europe’s citizens.

He also thanked the speakers for giving the audience such valuable insights into the issue of reporting of adverse drug reactions. He stressed that effective pharmacovigilance is essential, and that effective reporting is the basis of effective pharmacovigilance:

“The message is clear; we can no longer afford to accept a situation in which adverse drug reactions are underreported.”



Filip Babylon

Mr Babylon expressed the hope that the new legislation would go some way to making reporting easier by clarifying the procedures. But, patients and pharmacists, and of course other health professionals, must play their part. He reminded the audience that 75% of medicines are prescribed and dispensed in primary care settings, and that pharmacists will come into contact with many groups – such as children and the elderly, and those taking a number of medicines simultaneously – who do not take part in clinical trials. Out of all the health professions, pharmacists have the largest degree of interaction with European citizens.

Mr Babylon summarised the discussion of the day, pointing out that medicines bring vast benefits to our citizens and are in many respects the heart of health systems. He made it clear that pharmacists are ready to play their part in ensuring that, while no medicine is ever completely risk-free, their benefits are maximised and the risks minimised.





A final word from the sponsoring MEP...

"The PGEU/EPF lunch meeting brought together all the main stakeholders in the pharmacovigilance reform, and it was good to see so much excitement in the room about the upcoming changes.

The message that stood out in my mind was the reminder by June Raine of how far we have come. If the thalidomide tragedy had happened today, it would only take a handful of cases to actually identify the problem.

In the 1960s, it took thousands of affected births before the problem was picked up.

Implementation of the legislation will start soon, and we must keep an eye on this to make sure that the EudraVigilance database becomes fully operational as soon as possible, and the black symbol [to indicate medicines under additional monitoring] is chosen appropriately.

Also, some Member States may find it difficult at first to adapt to Direct Patient Reporting, but lessons can be learnt from countries where this is already a success."

Linda McAvan, MEP
September 2010

Information for Editors

The Pharmaceutical Group of the European Union (PGEU) is the European association representing community pharmacists. PGEU's members are the national associations and professional bodies of pharmacists in 30 European countries, including EU Member States, EEA members and EU applicant countries. For more information, please visit the PGEU website <http://www.pgeu.eu> or contact Ms Giovanna Giacomuzzi, PGEU Communications and Policy Officer (tel. +32 2 238 08 18).

The European Patients' Forum (EPF) is the umbrella organisation of European patient organisations active in the field of European public health and health advocacy. EPF currently represents 44 patient organisations, which are national coalitions of patient organisations and chronic disease-specific patient organisations operating at European level. EPF's vision is high-quality, patient-centred, equitable healthcare for all patients throughout the European Union. For more information, please visit the EPF website, <http://www.eu-patient.eu> or contact Ms Efstathia Megas, EPF Communications Officer (tel. +32 2 280 2334).