Dr Peter Arlett, Head of Pharmacovigilance and Epidemiology at the EMA, discusses the agency’s involvement in current and future EU pharmacovigilance activities. Interviewed by Raj K Bains, Consultant Editor, Regulatory Rapporteur

Introduction

Peter Arlett, MD, MRCP, FFPM, received his degree in medicine from the University College London (UCL) in 1991. His career steps include: hospital physician in Oxford and at the Hammersmith Hospital; 1996, MHR&A and 2001 UK delegate to the CHMP; 2003, Pharmaceuticals Unit, DG Enterprise and Industry, European Commission, 2004, honorary senior lecturer at UCL; 2008, EMA; 2004, ICH steering committee.

Q: EU pharmacovigilance operates in an exciting and fast moving environment. In this interview, I would therefore like us to condense and weigh the vast amount of information on EU pharmacovigilance and provide our readership with a current update. Let’s start with an easy question related to this topic. Since 1 September 2016, your Department at the European Medicines Agency (EMA) has been renamed, from “Pharmacovigilance” to “Pharmacovigilance and Epidemiology Department”. Why this name change?

A: The word “epidemiology” captures the core methodology to exploit real-world data in support of medicines regulation. In addition to coordinating EMA and EU pharmacovigilance, the Department will now be coordinating epidemiological methods and use of real-world data across the EMA’s activities.

Q: Our readership is very much interested in the future of the European pharmacovigilance system. Can you give us your view on how this might take shape?

A: In terms of scanning the horizon, I would like to share with you some of the drivers I see for 2017. The first area to highlight is that we need a planned, integrated approach to lifecycle drug development and surveillance. Second, timely access for patients to safe and effective medicines with surveillance and evidence generation underpinned by validated scientific methods; by that I’m talking about evidence-based regulatory sciences. Third, working with real-world evidence, ie, evidence based on data generated outside conventional clinical trials. Fourth, making best use of technology and harnessing the opportunities presented to us, for example by smartphones, new software, cloud technology and so on. Last but not least is the impact of pharmacovigilance on health promotion and prevention: we need to measure impact for specific products as well as pharmacovigilance processes to ensure we are effective and to drive process improvement. So in terms of looking forward, these are the key areas to focus upon. We also must not forget the environment we work in, and in my presentation given at the 10th Pharmacovigilance Stakeholder Forum back in September 2016, I called these “axes of influence”: namely, time, geographic, sectors, economic (cost), political, societal, technological and scientific. You may refer your readers to the Stakeholder Forum.1

Q: In the past, the regulatory process has mostly taken place between industry and regulators. Today, other stakeholders – patients, consumers, healthcare professionals (HCPs) and academia – are considered to be key to the regulatory process. This was for instance outlined in the EMA’s multi-annual work programme.2 Could you comment on how this broader concept of stakeholders is applied in pharmacovigilance?

A: In terms of patient involvement and patient engagement, I would like to make reference to Guido Rasi’s presentation at the aforementioned September 2016 Pharmacovigilance Stakeholder Forum. In his opening remarks he stated that pharmacovigilance and medicines regulation in general will need to focus more on the patient. In his view we need to invest in regulatory sciences which will underpin regulatory process improvement. We want to ensure that pharmacovigilance is fully utilised in a robust, planned and proactive way. In this way we can not only function as a protector of the patient from harm, but we can also act as an enabler for patients, helping them access medicines that fulfill their unmet medical needs. That puts the patient at the centre. Just to summarise, the EMA has put a lot of work and investment into the cooperation with patient organisations. The interaction is now very well structured. Patients are involved throughout the lifecycle of medicinal products. For policy questions we have the well-established Patients & Consumers Working Party (PCWP)3 where the EMA and European-level patient organisations discuss how to get the best out of involvement of the patient.

Product issues are not discussed within the PCWP. Rather, individual patients are consulted and, in addition, key committees including the PRAC [Pharmacovigilance Risk Assessment Committee] as well as advisory groups include patients as members. For example, if during the marketing application assessment, a pregnancy prevention programme is considered to manage the risk of exposure to a medicine, patients with the disease to be treated might be consulted on the feasibility of the programme being considered. Similar consultation can take place in the post-authorisation phase.

As with other committees within the agency, we have patients in our area as full members. The PRAC is a good example, where Albert van der Zeijden and Marco Greco are patient representatives with voting rights. Marco is the member and Albert is his alternate. From my experience they are very active PRAC members.

The last thing to mention in the patient engagement discussion is that, following a public consultation,4 in the second quarter of 2016 the PRAC adopted the rules of procedure on the organisation and
conduct of public hearings. In July 2016 we conducted a pilot run to test these procedures. The bottom line is that public hearings do what they say: they are about hearing the public, and the public will largely be patients. These hearings will be conducted in the context of important referrals and we would anticipate that the first hearing will take place in 2017 at the EMA. When the right topic comes up where we want to hear the patient voice in this way, we are ready to go. A public hearing is foreseen in the legislation and it’s to get more public involvement. The PRAC hearings will be particularly focused on patients, but there will also be representation of HCPs and industry.

Q: It is well known that the regulatory status of a drug is not of so much concern for HCPs; it is more about the accepted use by the medical community. How do you envisage engaging HCPs into the regulatory process?

A: It’s a good and valid question. We talked earlier about the PCWP: we also have an analogous group, the HealthCare Professionals’ Working Party (HCPWP) with the aim to foster collaboration. Again, this means working together with individual experts or representatives from European level societies, including professionals from different therapeutic areas or professional groupings and learned societies like oncology and rheumatology, community pharmacists and general practitioners. The whole point of the HCPWP is to strengthen the engagement with HCPs. For important therapeutic issues we have scientific advisory groups set up to hear the clinical experience of healthcare professionals. Further, I would like to mention that earlier in 2016 the agency consulted on an approach to better engagement with academia. Clearly, academia is a subset of HCPs. There are existing collaborations, but we need to strengthen and give more structure to the academic collaboration, because they are not established in all areas of the agency’s work. Actually in the area of pharmacovigilance we have significant academic collaboration, for example through regulatory science projects and the ENCePP [European Network of Centres for Pharmacopoeiology and Pharmacovigilance]. I’ll come back to ENCePP later.

The last point to make is that we acknowledge that regulation also covers a wider context. The regulatory domains of product label and product distribution are drivers, but we also need to understand that we have other factors such as health technology assessment (HTA), pricing and reimbursement, as well as professional freedom. Having good engagement with HCPs by working with the HCP associations helps to make sure that in the event of product issues, our regulatory messages get through. If you take a piece of action on a product after a referral, for example after the valproate referral [on risks of developmental disorders in children exposed in utero to valproate and related substances], there was work with HCPs to maximise the impact of the restricted label for use of products containing valproate. This took place through learned societies who were key in updating their respective guidelines. We understand that we don’t work in isolation.

We need collaboration with HCPs both at a policy level and at an individual product level.

Q: Could you speak about some of the recently completed and still ongoing pharmacovigilance projects that will shape the future of pharmacovigilance in Europe, including those with other European regulators, for instance the SCOPE joint action? I’m thinking here of projects in collaboration with industry and academia as well. Which of the numerous projects are important from your point of view? What has already been achieved in these projects and what is anticipated?

A: You mention SCOPE [Strengthening Collaborations for Operating Pharmacovigilance in Europe]; so let’s discuss SCOPE briefly. SCOPE has been really important and continues to be really important. SCOPE is very much from a member state perspective: “by the member states for the member states”. The SCOPE joint action aims to build capacity, strengthen pharmacovigilance and share good practices. The member states have welcomed the project enormously. There has been good collaboration and very active participation by the different member states. SCOPE formally closes in the second quarter of 2017. The EMA has collaborated closely with SCOPE and will support efforts to ensure the sustainability of the outputs, including sharing of best practice, training modules, ADR-reporting apps. One key sustainability factor will be the coordinated training through an EU Network Training Centre. It’s a collaboration between the national competent authorities and the EMA to ensure high-quality training for regulators. So the SCOPE pharmacovigilance outputs will be sustained through that. At the moment SCOPE is limited to the regulators. The current plan is to keep focus on training the regulators. So that’s SCOPE – important, welcomed, very strongly supported by the Member States and well-coordinated with the EMA work.

Further, we would like to highlight another example of project work: PROTECT [Pharmacopoeiologial Research on Outcomes of Therapeutics by a European ConsorTium]. The PROTECT project was initiated as a public-private partnership under the Innovative Medicines Initiative (IMI). IMI is a joint undertaking between the European Commission and the pharmaceutical industry association EFPIA. PROTECT is a really important project: it was a big project, co-led by the EMA, and it really focused on pharmacovigilance. The results are already changing the way we work at the EMA. For example, signal detection methods have already incorporated PROTECT results at the EMA: this relates particularly to the algorithms for statistical signal detection and the thresholds used for increasing the effectiveness and efficiency of signal detection. The great thing about the PROTECT project is that it has already given us results regarding the signal detection part. PROTECT also had a work stream on epidemiological methods, and there was a standalone dedicated issue of Pharmacopoeiology and Drug Safety presenting the results. These methods have already been incorporated into ENCePP scientific guidance very highly used by academia and industry. Another work stream of PROTECT focused on collecting information directly from patients. It showed that collecting data from patients, particularly through the internet on medication use in pregnancy, was a useful method for learning about lifestyle factors and how medicines are used during pregnancy. The final area was on benefit-risk assessment and patient values. This included visual representations in which benefits and risks are presented and communicated; really, state of the art. The work stream also investigated tabulation of benefits and risks rather than just describing them in a narrative. So maybe the headline of the PROTECT project is

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back to where I started: regulatory science underpins evidence-based process improvement. In other words, let’s not change things based on a hunch, let’s do research because that’s how we will be more effective at drug safety monitoring and in this way increase the effectiveness and efficiency of medicines regulation.

Just one other project I want to mention briefly is WEB-RADR. This project is again IMI-funded. It was launched in September 2014 for three years. The WEB-RADR project looks at ways of utilising new technologies and social media for pharmacovigilance purposes. Some examples are supported apps for smartphones (that can be used to report ADRs [adverse drug reactions] and get drug safety information) and utilising social media data. All very cutting edge. I mention WEB-RADR particularly because that’s something to look out for in 2017.

Q: Could you talk about the relations that the Pharmacovigilance and Epidemiology Department at the EMA maintains with bodies like the US FDA and WHO, but also industry? Are there any outcomes of these initiatives that you want to highlight?

A: In July 2015 there was an EMA press release on the back of the high-level strategic bilateral meeting with the FDA announcing further strengthening of the pharmacovigilance collaboration with the FDA. We in Pharmacovigilance and Epidemiology have very successful monthly product-related teleconferences on drug safety issues and product-related risks. We share with the FDA information either as assessment reports or we discuss assessment conclusions and communications. Our topics are mainly driven by the PRAC agenda. We also have shared communications, and communication plans. Additionally, over the last 12 months, Pharmacovigilance and Epidemiology has had quarterly strategic calls with the FDA. We are confident that over time, this effort will bear fruit and bring convergence and prevent divergence.

WHO is another nice example. I think the first thing to say is that we work very closely with WHO. Confidential arrangements are in place. We share confidential information with the WHO headquarters in Geneva and the Uppsala Monitoring Centre (a WHO collaborating centre) in Sweden. We routinely pre-warn each other on upcoming safety issues. Regarding the WHO, the next area which is important to mention is about the EudraVigilance access policy. In December 2015, we agreed the arrangements for sharing ADR data with the WHO. The data exchange will only be possible when the new EudraVigilance system goes live in 2017. From the fourth quarter of 2017, all EU ADR reports will be provided to the WHO, ie, ADR reports for all 31 member states, on a daily basis and in the new ISO ICH E2B R3 format. What else about WHO? The EMA is represented and while some topics are raised by regulators, the majority are raised by the industry. This has been running for a couple of years now and has proven to be very fruitful, very collaborative. It’s been welcomed on both sides. Since mid-2014, we have published a quarterly UPDATE document which focuses on “What’s new in pharmacovigilance”, specifically for MAHs [marketing authorisation holders]. It shares information related to specific areas of business change, information on the development of the enhanced systems and services, essentially helping MAHs prepare for the business change to come. Again, the feedback that we’ve had has been positive.

The other areas to emphasise in terms of industry are the public-private partnerships. The keyword there is partnership around a common research question. The way it works is that there are public calls from the IMI. From the bids, an academic consortium is selected. The consortium is then put together with an industry consortium to make the partnership. For most of the public-private partnerships, the public part has been led by academia. There are a few examples, PROTECT being one of them, where the public part was regulator-led, in that case, by the EMA.

Q: Could you discuss how pharmacovigilance at the EMA collaborates with, or even fosters, academic research? I’m thinking here of topics like EudraVigilance data availability for researchers or funding, or the new buzzword “big data”?

A: The first thing I would mention is ENCePP because it’s been a really important initiative. ENCePP is now already nine years old. ENCePP has been established by the EMA in collaboration with the EU regulatory network as an expert network with the aim to build the EU capacity for the delivery of post-authorisation studies (PAS). It is coordinated by the EMA at the EU level: done through networking, through sharing best practice, through introducing a code of conduct for governance aspects, and also through supporting the conduct of high-quality independent post-authorisation studies through methodological guidance by the EMA. Through ENCePP, the agency has provided a lot of support to the academic partners to strengthen the monitoring of the benefit–risk balance of medicinal products in Europe.

Just a couple of other things to mention. We have revised the EudraVigilance access policy. It was adopted by the EMA Management Board in 2015. It foresees that when the EudraVigilance system goes live in 2017, even greater access to the EV data will be made available to researchers. All personal data will still be fully protected. The researcher makes a request and we’ll provide anonymised data – you won’t be able to identify individual patients but you will be able to conduct public health research.

Regarding funding of research. Clearly, funding of research is a big topic. There’s private funding from industry, and there’s public funding and there are public-private funding partnerships. Industry is still the major funder of medicines research, be it clinical trials or observational studies. In terms of public funding at national level there are all sorts of different models. At the European level, the biggest player is IMI 2. This public-private partnership is funded by Horizon 2020, the European Commission’s framework programme for research and innovation, and by "in kind" contributions from EFPIA. In other words, the pharmaceutical industry will provide resources, like for instance human resources or IT infrastructure. In terms of your specific question on funding for academic research, the public funding of IMI 2 goes to the academics as well as to SMEs [small and medium-sized enterprises]. Nevertheless, the vast majority of the funding is going to academics.

Just one other thing we might highlight under funding: there is a lot of scope for industry collaboration on specific studies. Regulators are encouraging industry to do joint studies. A few nice examples are studies on sodium valproate, domperidone, and cyproterone with ethinyl estradiol. These are all joint studies post referral. The whole
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Point is that these efforts are jointly undertaken by the brand leaders and the respective generic companies. I won’t go into the details of the studies but the key point is that in each case, the pharmaceutical industry collaborated, funded and ran a programme of studies rather than individual companies duplicating studies.

You mention in your question “big data”. It would be worth highlighting that on 14–15 November 2016, the EMA hosted a really important event listening to those that are at the cutting edge of “big data”. You can access the slides and the broadcast online.24

Q: Who is at the cutting edge?

A: Well, that’s very interesting; there are a lot of academic groups, technology companies, and certain pharmaceutical companies that are putting a lot of time and effort into this topic of “big data”. Regulators are also focusing on real-world evidence. One of the reasons that we have organised this event is that it’s important for us to know what’s going on out there, as there will be important implications for medicines regulation. We don’t just follow them, we embrace them. I would say the workshop was largely a listening exercise for the regulators.

Q: From your point of view, what are the upcoming challenges for pharmacovigilance as a regulatory science?

A: I’ll just give you some headlines regarding your question, if you like. Perhaps, studies that look at both the effectiveness and the safety of medicines. Perhaps, realising the potential of real-world evidence, and the role and utility of social media data. Perhaps, the regulatory science underpinning the collection of data in cycles, once a product is on the market (some would call this rapid cycle analytics); but also the logistics of getting access to these data. Perhaps one other area I would like to highlight is the science of measuring the impact of pharmacovigilance activities. I see this as having three branches: one area is the impact of individual processes like ADR reporting. The second area is the impact of individual product risk minimisation, for example a pregnancy prevention programme. The third area is engaging with HCPs and patients. Pharmacovigilance needs to be relevant in the regulatory process and the decisions need to be science-based and we need methods for measuring all of that. We held a public workshop on 5th and 6th December 2016 which looked specifically at the scientific methods to measure the impact of pharmacovigilance activities.25

Q: Following on from the previous question, new regulatory strategies like the “adaptive pathways” approach are currently being discussed. Pharmacovigilance plays an important role in these models. How do you anticipate that this changes the involvement of pharmacovigilance in the registration process?

A: If I step back from this question and go one step higher and ask what is the role of pharmacovigilance in the registration process: The whole point of adaptive pathways is a more lifecycle approach to the authorisation and management of medicines.26 We would say pharmacovigilance is core to robust and proactive medicines regulation and it’s all about planning. It’s about planning during drug development, it’s about planning at authorisation and it’s about planning the post-authorisation phase. In the drug development phase the planning is delivered through scientific advice. We recently strengthened scientific advice on post-authorisation safety studies (PASS) and made strong links between the Scientific Advice Working Party and the PRAC.27 Planning at authorisation and post-authorisation is through the EU-RMP and we are strengthening this risk management planning. We would hope that by Q1 2017, we will have the final revised guidance on risk management planning. We want to be proportionate and effective for public health. The last thing which is critical in terms of supporting the authorisation of new products is that we have the capacity to monitor products including for observational research and real-world evidence. I mentioned ENCePP earlier as an example.

Q: As you know, TOPRA is an organisation that represents individual regulatory affairs professionals. One of the foci of TOPRA is the continuous professional development (CPD) of its members. What, in your opinion, will be the future pharmacovigilance-related challenges for regulatory affairs professionals themselves, and how can they best prepare?

A: This is about TOPRA and the regulatory professionals within TOPRA. I think we’ve acknowledged there is a lot going on. Pharmacovigilance has evolved rapidly and the evolution continues. It should never stop, because if it stops, then we are not having evidence-based process improvement. In that case we would not be responding to the changes and drivers that we discussed in the previously mentioned September 2016 Stakeholder Forum. So I think it’s worth mentioning that regulatory science is very active in the area of pharmacovigilance and will be a key driver for change. One last thing to say is that our collaboration with the regulatory network in terms of making quality information available and establishing dialogue is of high priority. Here, we see TOPRA as one of our key stakeholders. Just as an example of the kind of events that will continue in 2017, there will be a number of workshops. These are about making sure there are opportunities for input from regulatory professionals.

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