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Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee

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This journal has previously reported on initiatives to increase proactivity in the surveillance and management of drugs on the market and considered how this might influence drug (medicinal product) development programmes (*Nature Rev. Drug Discov.* **11**, 255 (2012))[1]. We now report on the implementation of a new European Union (EU) initiative to improve the promotion and protection of public health through better planning for, and management of, drugs on the market.

The new EU pharmacovigilance legislation became operational in July 2012, and after 18 months of operation we suggest that this initiative is starting to demonstrate results in terms of patient safety, and that there could be wider implications in terms of more safe and effective drugs being made available in the future[2,3].

The new legislation is centred on the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA). The PRAC was formally established in July 2012 and its membership was completed in spring 2013 with the appointment of patient and healthcare professional organization representatives as full voting members. The Committee includes independent experts in pharmacoepidemiology, clinical pharmacology, biologics, signal detection, risk communication and vaccine vigilance.

The PRAC has a broad remit covering all aspects of pharmacovigilance, including risk management planning and post-marketing benefit–risk assessment. Its mandate includes specific reference to the fact that risk management and assessment should be pursued with due regard for the therapeutic effect of the medicinal product. The PRAC mandate also places a strong focus on the Committee's role in the design and evaluation of post-authorization studies to ensure they contribute meaningfully to sustainable life-cycle benefit–risk management. Just as the EMA works within the European regulatory network of national drug agencies, the PRAC provides its advice and recommendations to the network, and for many procedures these recommendations are considered by the Coordination Group or the Committee for Medicinal Products for Human Use (CHMP) before they become legally binding (see the EMA website for further information on the PRAC).

All applications for drug marketing authorizations now have to, by law, include a risk management plan (RMP) documenting the proposed risk management system to be implemented if a marketing authorization is granted. The PRAC is systematically consulted in the risk management planning for all new innovative drugs and for important changes to existing drugs that pose challenges in the optimization of their safe and effective use.

In the first 18 months of its operation, the PRAC has considered risk management plans for 160 medicinal products. In this work the PRAC has focused on ensuring feasible, evidence-based and risk-proportionate planning[4].

The collection of individual reports of suspected adverse drug reactions (ADRs) is one of the foundations of drug surveillance, and the reporting rules have been strengthened. These now include the formal introduction of patient reporting in all EU member states (to enable patient engagement), the provision of instructions on reporting in drug leaflets for patients, as well as the labelling of new drugs and those under close safety surveillance with a black triangle symbol indicating the need for enhanced reporting.

The data shown in FIG. 1a indicate an overall increase in reports received from the European Economic Area (EEA) in the first year of operation of the new legislation, and a proportionately greater increase in patient reporting. More and better-documented spontaneously reported suspected ADRs, together with results from studies (interventional and non-interventional), provide key data and information inputs for signal detection. The PRAC has a crucial role in the prioritization of potentially new or changing safety issues (safety 'signals') and in making recommendations on the management of these — for example, for further investigation or for drug labelling changes. FIGURE 1b shows the number of signals evaluated by the PRAC in its first 18 months and, for the completed evaluations, the number that resulted in recommendations for changes in drug labelling. The results demonstrate that by prioritizing and evaluating signals, the PRAC is able to ensure that new or changed safety issues can be translated into drug labelling updates, including new restrictions on use and advice on optimal drug use.

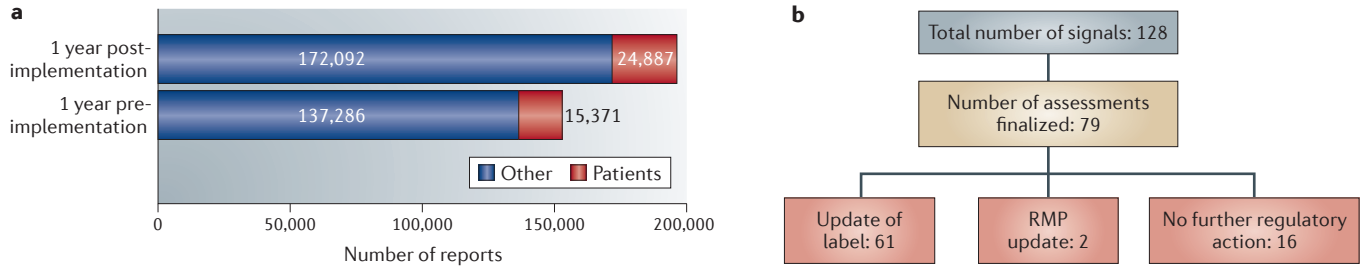

Figure 1 | **Impact of the new European legislation on pharmacovigilance.** **a** | Number of cases of spontaneous reports of adverse drug reactions within the European Economic Area in the 12-month periods before or after the implementation of the legislation in July 2012. **b** | Number of safety signals evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC) in its first 18 months and the outcomes of the finalized evaluations.

Although signal evaluations usually focus on one or a small number of specific ADRs, more global risk or benefit–risk assessments of a drug or group of drugs take place through assessments of Periodic Safety Update Reports (PSURs; also referred to as Periodic Benefit Risk Evaluation Reports)[5] or EU Pharmacovigilance Referrals. Both types of assessment procedures are conducted by the PRAC and both result in legally binding outcomes, following specified procedural steps that are conducted within timeframes laid down by law. These outcomes can range from a requirement for further study to drug labelling changes or drug restrictions and withdrawals. In the 18 months from July 2012, the PRAC has considered and issued recommendations on 486 PSURs and 22 Referrals have been initiated. Of the latter, 13 have had a Coordination Group or CHMP decision in the same timeframe. TABLE 1 lists the outcomes and time from initiation to decision for these.

The data show an average time of 6.4 months for the finalization of these Referrals. This indicates that the PRAC has rapidly operationalized new practices and processes to support timely, high-quality assessments to optimize the safe and effective use of medicines though drug labelling changes and, when necessary, restrictions.

Transparency in the regulation of medicines is considered to be crucial in allowing stakeholders to follow and engage in the processes, to understand the rationale and evidence supporting recommendations and actions affecting drugs and care, and in building trust. To this end, a key aim of the new legislation is to increase transparency, and this has included making suspected ADR data publicly available (see the EMA's European database of suspected adverse drug reaction reports for further information) and ensuring public posting of post-authorization studies, with 202 studies posted up to January 2014 in the EU PAS Register. The work of the PRAC has been characterized by an unprecedented level of transparency before, during and after the meetings, with real-time publication of agendas, meeting highlights, notifications of referrals, lists of questions and minutes.

The PRAC has placed an emphasis on the importance of strengthening the science base for regulatory decision-making, continuing efforts to ensure efficient management of workload and optimized use of regulatory tools, and further increasing stakeholder engagement, with the overall objective of delivering strengthened public health promotion and protection. The PRAC ensures its decision-making is supported by robust and timely assessment based on all relevant evidence and drawing on the best available expertise[6]. The PRAC's focus on efficiency, combined with quality, is achieved through improvement of processes based on measurement and analysis and, where appropriate, based on evidence from regulatory sciences[7].

Looking forward, the EMA, its scientific committees and the EU regulatory network are focusing on efficiency and simplifications to free up resources that can then be reinvested to deliver more for public health. Initiatives include: the development of a literature monitoring service by the EMA to negate the need for companies to conduct duplicative literature reporting; further development of the EU system for reporting and analysing ADRs (EudraVigilance) to

Table 1 | **Finalized PRAC referrals from July 2012 to December 2013**

Drug or drug group	Issue	Started	Finalized	Outcome	Duration
Codeine	Use in children	October 2012	June 2013	Change to product labelling (variation)	8 months
Diclofenac	Cardiovascular safety	October 2012	June 2013	Change to product labelling (variation)	8 months
SABAs (short-acting beta agonists)	Use in pregnancy	November 2012	October 2013	Change to product labelling (variation)	11 months
HES (hydroxyethyl starch solution)	Risks of renal injury and mortality	November 2012	October 2013	Change to product labelling (variation)	11 months
Almtrine	Risks of peripheral neuropathy and weight loss	November 2012	May 2013	Product withdrawn (revocation)	6 months
Laropiprant/nicotinic acid	Negative benefit–risk balance	January 2013	January 2013	Product withdrawn (suspension)	3 weeks
Tetrazepam	Serious skin reactions	January 2013	April 2013	Product withdrawn (suspension)	3 months
Medicines containing cyproterone acetate (2 mg) and ethinylestradiol (35 mg)	Risk of thromboembolism	February 2013	May 2013	Change to product labelling (variation)	3 months
Combined hormonal contraceptives	Risk of thromboembolism	February 2013	November 2013	Change to product labelling (variation)	9 months
Flupirtine	Hepatotoxicity	March 2013	June 2013	Change to product labelling (variation)	3 months
Nicotinic acid and related substances (acipimox, xantinol nicotinate)	Negative benefit–risk balance	March 2013	December 2013	Change to product labelling (variation)	9 months
Kogenate Bayer/Helixate NexGen	Inhibitor formation	March 2013	December 2013	Change to product labelling (variation)	9 months
NUMETA G13%E, NUMETA G16%E emulsion for infusion and associated names	Magnesium overdose	June 2013	September 2013	Suspension of one formulation; change to product labelling (variation) of the other	3 months

PRAC, Pharmacovigilance Risk Assessment Committee.

allow simpler reporting for industry and better data analysis; and the development of a central reporting, storage and access system for PSURs from industry to simplify their reporting and analysis.

These are early days for the operation of the new EU pharmacovigilance legislation and the establishment of the PRAC as a public health body. Early signs, however, based on process indicators such as those reported here for RMPs, ADRs, signals, PSURs and EU Pharmacovigilance Referrals, point to more systematic and proportionate risk management planning, the promotion of reporting (including from patients), greater coordination of real-time signal management, faster assessment and decision-making, and thus strengthening of the link between pharmacovigilance assessments and regulatory actions such as labelling changes to optimize safe and effective drug use.

Finally, how could proactivity in the surveillance and management of drugs on the market influence drug development programmes? After 18 months of operation of the PRAC, we suggest that more safe and effective drugs can be made available through planning, engagement and transparency, as well as rapid assessment and regulatory action. Proactivity and effectiveness in the surveillance and management of drugs on the market increases stakeholder confidence in medicines regulation and, at the time of authorization, also increases the confidence of regulators that any gaps in knowledge can be robustly addressed once the product is on the market. This is further supported through transparency measures for building public trust. In summary, proactive, effective and transparent pharmacovigilance, leading to confidence and trust, supports product development to fulfil unmet medical needs and helps ensure that any knowledge gaps are addressed in a timely manner and in the best interests of public health[8].

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1. Mullard, A. Unleashing the Mini-Sentinel. *Nature Rev. Drug Discov.* **11**, 255–257 (2012).
2. European Medicines Agency. EMA recommends 81 medicines for marketing authorisation in 2013. *European Medicines Agency* [online], http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/01/news_detail_002006.jsp&mid=WC0b01ac058004d5c1 (2014).
3. Eichler, H. G. *et al.* Adaptive licensing: taking the next step in the evolution of drug approval. *Clin. Pharmacol. Ther.* **91**, 426–437 (2012).
4. Prieto, L. *et al.* Evaluation of the effectiveness of risk minimization measures. *Pharmacoepidemiol. Drug Saf.* **21**, 896–899 (2012).
5. International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Periodic Benefit-Risk Evaluation Report (PBRER) E2C (R2). *ICH* [online], http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf (2012).
6. Arlett, P. *et al.* The European Medicines Agency's use of prioritised independent research for best evidence in regulatory action on diclofenac. *Pharmacoepidemiol. Drug Saf.* **23**, 431–434 (2014).
7. Arlett, P. & Kurz, X. New approaches to strengthen pharmacovigilance. *Drug Discov. Today Technol.* **8**, e15–e19 (2011).
8. Eichler, H. G. *et al.* The risks of risk aversion in drug regulation. *Nature Rev. Drug Discov.* **12**, 907–916 (2013).

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
EMA Pharmacovigilance Risk Assessment Committee (PRAC): http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18
EudraVigilance: https://eudravigilance.ema.europa.eu/highres.htm
EU PAS Register: http://www.encepp.eu/encepp_studies/indexRegister.shtml
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