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Workshop: measuring the impact of pharmacovigilance activities

Workshop report

5 - 6 December 2016
European Medicines Agency, London, United Kingdom

Measuring the impact of pharmacovigilance activities: European Medicines Agency workshop calls for coordinated EU approach

Recommendations to develop a framework for impact evaluation

Executive summary

Pharmacovigilance systems have been established to monitor the safety of authorised medicinal products and to detect and manage any change to their risk-benefit balance. The European Union (EU) has one of the most advanced pharmacovigilance systems and national competent authorities in collaboration with the European Medicines Agency (EMA) and the European Commission share a responsibility to ensure that key pharmacovigilance activities and processes are effective and efficient and to continuously improve the EU pharmacovigilance system to achieve highest standards of public health protection, safe use of medicinal products, and to monitor the outcomes of risk minimisation measures. This can only be delivered by measuring the impact of pharmacovigilance activities.

This workshop was an excellent opportunity to bring together the available expertise from partners and stakeholders, including regulatory and public bodies, healthcare-professional and patient-consumer organisations, academia and the pharmaceutical industry, and was attended by more than 150 participants. The workshop was broadcast live and a recording is available here.

The workshop's objective was to explore methods for impact research and to identify enablers and barriers to measuring the impact of pharmacovigilance. Particular focus was on methodologies for measuring the impact of product-specific regulatory actions in terms of public health outcomes, as well as the impact of individual pharmacovigilance processes.

The workshop was organised in five sessions. The first two plenary sessions focused on the need for measuring the impact of pharmacovigilance from a public health perspective and on international approaches to measuring impact of regulatory decisions. Three parallel, interactive breakout sessions explored enablers and barriers for patient and healthcare professional engagement, methodologies for measuring health outcomes of regulatory outputs and measures of the impact of pharmacovigilance processes. Based on the findings from the breakout sessions the plenary then discussed methodological gaps and observations and concluded with a summary of key recommendations to further progress the implementation of the PRAC impact strategy.

The workshop reinforced the clear need to measure the impact of pharmacovigilance activities based on evidence which allows regulators and pharmaceutical industry to refocus resources to strengthen the current pharmacovigilance system's capability for most efficient public health protection. There was broad consensus that all stakeholders of pharmacovigilance have a responsibility to contribute to measuring the impact of regulatory decisions. At the same time the PRAC impact strategy's approach was tested and a number of proposals and recommendations were made to streamline ongoing initiatives from regulators, academia, patient and healthcare professional organisations and industry at national and international level.

The key pillars of impact evaluation are robust scientific methodologies, a sustainable framework for the generation of decision-relevant data that is integrated into regulatory procedures, timely delivery of results and clear roles and responsibilities. Innovative risk minimisation measures and balancing the

benefits and risks of medicines are important steps towards patient empowerment to achieve the best public health outcomes. All participants acknowledged that depending on the outcomes of pharmacovigilance impact assessment the future system needs to be flexible and adapt to change.

As a way forward a modified strategy with a more systematic public health focus was discussed. Such an approach would allow regulators to determine to what extent planned regulatory action will affect public health outcomes and inform ongoing and future decision making. Such approach requires closer collaboration and synergies to be leveraged amongst all stakeholders of pharmacovigilance. As a key stakeholder pharmaceutical industry expressed its commitment to contribute and share existing data relevant for impact research and to collaborate with regulators, patients and healthcare professional organisations, and academia to generate the evidence needed to measure impact.

The workshop also underlined several shortcomings of traditional pharmacovigilance processes and their contribution to public health protection, e.g. regulatory and operational challenges of survey studies measuring the effectiveness of product-specific risk minimisation and feasibility of post-authorisation safety studies. A number of practical and methodological challenges of impact research relate to external factors (e.g. different national healthcare policies) which influence how regulatory measures taken at EU level are implemented locally. These uncertainties are yet to be addressed and integrated in future decision making processes.

This workshop offered an excellent opportunity to gather expertise in the area of impact measurement and to discuss methodologies for modelling health outcomes of pharmacovigilance activities. The workshop concluded with the following six key recommendations which are further detailed at the end of this report (see page 25):

Key recommendations
1. Revision of the framework for impact evaluation
2. Systematic collection of impact relevant data considering the need for, the nature of and the approach to collection
3. Robust methodologies for measuring health impacts of pharmacovigilance activities
4. Establishing collaboration with novel information technology providers
5. Active engagement and capacity building with patient communities and healthcare professional bodies to support impact research
6. Development of a process for identifying relevant intended (and unintended) public health outcomes of regulatory decisions

Introduction

EU pharmacovigilance systems have been established to fulfil the tasks and responsibilities of EU pharmacovigilance legislation, to monitor the safety of authorised medicinal products and to detect and manage any change to their benefit-risk balance. Pharmaceutical companies and regulators have access to a variety of post-marketing surveillance tools that allow for systematic monitoring of the benefits and risks of medicinal products throughout the life-cycle. Pharmacovigilance activities include risk management planning and the detection, assessment, evaluation and management of drug-related adverse effects and the conduct of post-authorisation safety and efficacy studies. They are designed to prevent harm caused by medicines and to enable their safe and effective use and to inform regulatory actions. These regulatory actions may include

- informing healthcare professionals and patients of newly emerging information on the safety or effectiveness of a medicine,

- advising healthcare professionals, patients and carers to take action to modify their behaviour in order to prevent or minimise adverse reactions,

- restricting access to medicines when the benefit-risk profile of a product is no longer positive for a certain patient population, or

- a combination of these actions.

In January 2016 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted a strategy[1] for measuring the impact of pharmacovigilance activities which relies on a collaborative approach between stakeholders. Measuring the impact of key regulatory actions will allow those responsible for pharmacovigilance to determine which activities are most successful and to identify enablers and barriers for generating positive health impacts. Together, these will contribute to the further development of proactive pharmacovigilance systems and to promote best practice amongst stakeholders of pharmacovigilance across the EU.

Opening session

After the workshop was opened by Prof. Guido Rasi, Executive Director of the EMA, Dr. Xavier Kurz, Head of Surveillance and Epidemiology, set out the goals of the meeting. The primary objective was to explore methods in impact research and to identify enablers and barriers to measuring the impact of pharmacovigilance activities to support the EU regulatory network's legal mandate to continuously develop pharmacovigilance systems and ensure regulatory actions are effective and efficient. With the following secondary objectives the workshop aimed to facilitate the implementation of the PRAC strategy for measuring the impact of pharmacovigilance activities:

- Development of methodologies for measuring the impact of product-specific pharmacovigilance activities on clinical practice and health outcomes

- Methods to measure the impact of routine pharmacovigilance processes

- Fostering stakeholder collaboration

- Identification of enablers and barriers for generating positive impacts

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[1] Pharmacovigilance Risk Assessment Committee. PRAC strategy on measuring the impact of Pharmacovigilance activities (EMA/790863/2015).

Session 1: Importance of measuring the impact of pharmacovigilance

In the key note lecture **Dr. June Raine**, Medicines and Healthcare products Regulatory Agency, outlined the PRAC vision of pharmacovigilance impact research and how this new approach will strengthen EU pharmacovigilance systems. Monitoring the benefits and risk of medicines throughout the life-cycle is at the core of pharmacovigilance and risk management activities and aims to ensure a positive benefit-risk balance is maintained. However, regulators also need to ensure these activities are effective. Measuring impact of regulatory decisions is the missing piece of the regulatory jigsaw and highly relevant for important public health decisions that are aimed at reducing the public health burden of adverse drug reactions (ADRs), which account for considerable morbidity, mortality, and economic burden[2]. Considering that 20% to 70% of ADRs are preventable, regulators need to ensure that risk minimisation activities put in place to reduce the burden of ADRs are effective, otherwise alternative risk minimisation strategies may be required. The majority of ADR-related hospital admissions occur with the use of older medicines such as NSAIDs, diuretics, warfarin, ACE-inhibitors, antidepressants, beta-blockers and opiates, and not with novel or advanced therapy medicinal products. The new legislation places a legal obligation on regulators and the pharmaceutical industry to measure the effectiveness of risk minimisation in collaboration with patients and healthcare professionals.

Impact measurement has seen a regulatory evolution with the excellence in pharmacovigilance model, the ICH E2E guideline on pharmacovigilance planning in 2004, the introduction of EU risk management systems in 2005 and the EU pharmacovigilance legislation implemented since 2012. The culture of continuous scientific development based on best evidence and health outcomes as measurable public health benefits is not new. A number of major regulatory interventions have been subject to impact research and past experience has identified key challenges in relation to the uptake of regulatory measures, defining measurable public health impacts and the intended and unintended therapeutic consequences of regulatory decisions at local healthcare level.

The key pillars of impact evaluation are robust scientific methodologies, a sustainable framework for the generation of decision-relevant data integrated in regulatory decision-making, timely delivery of results and clear roles and responsibilities. The following examples demonstrate how the EU regulatory network's ability for measuring impact could be further strengthened. To reduce the risk of paracetamol overdose toxicity, pack size limitations and warnings in the patient information leaflet were aimed at balancing access in 2004. Concerns of switching to other analgesics were addressed in a study[3] published in 2013 which provided robust evidence that the restriction had an overall public health benefit in England and Wales.

In another example, accumulating data from studies showing impaired cognitive function in children exposed to antiepileptic drugs in utero, PRAC recommended as the outcome of a referral procedure in 2014 to restrict valproate use in pregnant women and women of childbearing potential with epilepsy, migraine or bipolar disorder. The variation of patient exposure by country and indication presented challenges to measuring the impact of this regulatory intervention which could therefore best be addressed locally. In the UK, prescribing rates have declined before the referral was completed; however one quarter of surveyed healthcare professionals had not received information about this restriction. For valproate, decision relevant data was generated to provide evidence on prescriber awareness, prescription rates and exposure data to monitor the impact in clinical practice.

A third example was a rapid observational study of the safety of pertussis vaccination in pregnant women in the UK which showed no evidence of an increased risk of stillbirth or other adverse effects

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[2] Pirmohamed M. et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ 2004; 329:15-19
[3] Hawton K. et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ 2013; 346:f403

post-vaccination. The results allowed regulators to remove the restriction of not using the vaccine in pregnancy which resulted in a significant decrease of pertussis cases in infancy.

The regulatory action for osteonecrosis of the jaw (ONJ) associated with intravenous bisphosphonates and denosumab in 2014 was an important trade-off of risks and benefits, and a good example of shared allocation of responsibilities. Based on EudraVigilance spontaneous data PRAC recommended to introduce further measures to minimise the risk of ONJ with a clear role for osteoporosis patients to be vigilant for signs and symptoms, but also responsibilities for dentists and oncologists to minimise the risk of ONJ.

Measuring the impact of regulatory interventions on patients' and healthcare professionals' knowledge, attitude and behaviour is a new domain which needs to be further explored since a lack of awareness and motivation on one hand and information overload on the other can significantly limit risk minimisation efforts in clinical practice. Regulators need to address these constraints and adapt to the findings of impact research as highlighted by the European Commission's report on pharmacovigilance activities[4], which identified a number of shortcomings e.g. in patient information leaflets but also the need for closer collaboration and engagement with patients and healthcare professionals to assess the impact of regulatory actions.

In conclusion, there is substantial experience in measuring impact and the PRAC strategy takes this approach to the next level, leveraging existing resources in Member States. However, methodological and strategic questions still remain to be addressed and this can only be achieved in a coordinated and collaborative approach of all stakeholders involved in pharmacovigilance and requires a framework for systematic monitoring of the impact of regulatory actions.

Dr. Dolores Montero, Spanish Agency of Medicines and Medical Devices, provided insights into regulatory initiatives of measuring the impact of pharmacovigilance. Whether risk minimisation measures reach their intended objectives and the target population has been examined in a survey of more than 3,600 healthcare professionals conducted in 9 EU countries under the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action[5]. The survey focussed on the knowledge, preferences and attitudes in relation to risk minimisation tools at EU level and respondents indicated awareness and receipt of direct healthcare professional communication (DHPC) (90%), national communication initiatives (87%) and educational materials (66%). In terms of trust in the sender the survey showed that regulatory agencies and professional bodies are the most trusted sources in contrast to lay press and pharmaceutical industry. The results highlighted that safety communication and the choice of dissemination channels can be further improved and alternative communication means considered whereas email and point of care alerts in electronic prescription systems ranked highest and mobile apps, TV/radio and phone calls ranked lowest.

The importance of measuring the impact of risk minimisation measures at national level was demonstrated based on learning from three EU referral procedures. Following the EU-wide withdrawal of the muscle relaxant tetrazepam in 2013 due to serious skin reactions the use of diazepam increased as an unintended consequence of the withdrawal in Spain. This shift to diazepam, which bears a higher risk of dependency and of withdrawal symptoms due to a longer half-life, was seen in drug utilisation data from the Spanish BIFAP[6] database after the first communication by the Spanish Medicines Agency at the start of the referral. The second example concerned cyproterone/ethinylestradiol products where the indications were restricted due the risk of thromboembolism. A survey conducted by the marketing authorisation holders of concerned products in different Member States showed that physicians were

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[4] European Commission. Pharmacovigilance related activities of Member States and the European Medicines Agency concerning medicinal products for human use (2012-2014).COM (2016) 489 final. Available at http://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/pharmacovigilance-report-2012-2014_en.pdf
[5] http://www.scopejointaction.eu
[6] Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (http://www.bifap.org)

well aware of the approved indication (moderate to severe acne) and unapproved indications (mild acne and contraception) which provided reassurance that the safety communication had reached healthcare professionals. Drug consumption data from Spain's national healthcare system further confirmed the already decreasing trend in the use of cyproterone acetate/ethinylestradiol, however an in-depth analysis of BIFAP data linking prescription data with electronic health records showed that after the referral the use for contraception was still higher compared to acne, which demonstrated that other factors (e.g. national reimbursement rules, clinical guidelines etc.) may have impacted prescribing behaviour. The third example focused on the usage of high doses of ibuprofen and dexibuprofen in patients with cardiovascular risk factors to better understand how medicines are used in clinical practice to tailor risk communication accordingly. Analysis of BIFAP data showed that in relative terms ibuprofen use in higher doses was low compared to the more potent dexibuprofen and this fact could be taken into account in evaluating regulatory action.

In summary, national experience in measuring the impact of regulatory actions clearly demonstrated that there is a need to tailor regulatory communications to the receivers' preferences. Regulators need to consider the therapeutic context, how medicines are used in clinical practice under specific national circumstances which influence the update of regulatory measures.

Dr. Thomas Goedecke, European Medicines Agency, presented the PRAC strategy for measuring the impact of pharmacovigilance activities. The strategy aims to systematically gather data and knowledge on the effects of measures and processes meant to ensure the safe use of medicines for patients. EU pharmacovigilance activities are designed to monitor the safety of medicinal products in clinical use and to detect and manage any change to their benefit-risk balance. Regulators and pharmaceutical industry have a legal responsibility to monitor the outcomes of risk minimisation measures and to continuously develop pharmacovigilance systems to ensure they are effective and efficient. The tools applied throughout the product life-cycle include the collection and management of ADR reports, the detection and management of safety signals, proactive planning of risk-minimisation measures and of post-authorisation studies to generate real world data on the use of medicines. Measuring the impact of these activities in terms of health outcomes is an iterative process based on scientific evidence to understand whether the measures taken to minimise the risks of a medicine have been effective and for regulators to determine which activities are most successful to promote best practice and further improve pharmacovigilance.

The PRAC strategy is based on four pillars: *i)* effectiveness of pharmacovigilance processes, *ii)* effectiveness of product-specific risk minimisation, *iii)* stakeholder engagement as enabler of effective pharmacovigilance and *iv)* collaboration on methodologies. The strategy's approach is underpinned by stakeholder collaboration, particularly with patients and healthcare professionals but also with academia through the European Network for Pharmacovigilance and Pharmacoepidemiology (ENCePP) and industry to assess whether or not pharmacovigilance activities do achieve their intended public health objectives at various levels. Health impacts can be measured e.g. by estimating patient and healthcare professional knowledge of risks following safety communication, changes in behaviour and changes in morbidity or mortality before and after a regulatory intervention. If not available, such data could be generated through modelling health impacts of regulatory interventions based on population-attributable risks, prevalence of exposure or behavioural changes.

In 2016 criteria for prioritising topics for collaborative impact research were developed which take into account the public health importance of regulatory actions, the potential impact in clinical practice and whether an impact study could deliver decision relevant data beyond the evidence generated through routine or additional pharmacovigilance activities (e.g. post-authorisation safety studies) from marketing authorisation holders.

Session 2: Approaches for measuring impact of pharmacovigilance and regulatory decisions

Dr. Gerald Dal Pan, United States Food and Drug Administration (FDA), presented the FDA experience with measuring the impact of pharmacovigilance. Impact assessment in this context looks at how well the current systems achieve its objectives, how efficiently they work and how well resources are allocated to determine any beneficial impact on public health. A review of all safety related label changes in 2010 examined the sources of data contributing to the label change and found that over 50% derived from spontaneous reporting, the resource-intensive backbone of pharmacovigilance. Other sources such as clinical trial data and pharmacoepidemiological data were also important but not to the same extent as spontaneous reporting. Boxed warnings were more frequently initiated by FDA compared to other label changes. To understand which product the patient actually took (i.e. the innovator brand or the generic) drug utilisation patterns of five antiepileptic drugs before and after generic introduction were examined which showed that the predominant reporting source after generic introduction was still the brand leader. However, a review of the reports showed that in 84% of cases the medicines that the patient actually took could not be identified and reporting seems to be directed to the brand manufacturer even if the patient did take another generic product. Another recent study systematically assessed the impact of scheduled post-marketing safety summary analyses on regulatory actions for a cohort of newly approved products as required by US law. The results showed that the majority of scheduled analysis did not indicate a signal and that these signals, when identified, accounted for only a small proportion (1.6%) of safety-related label changes for this cohort of products. However, the resource effort to conduct these analyses was disproportionately large.

The external effects of pharmacovigilance, i.e. how label changes actually promote the safe use of medicines was demonstrated by the example of cisapride where a boxed warning in 1998 contraindicated certain concomitant medications causing life-threatening cardiac arrhythmias. This regulatory action was accompanied by a DHPC at that time. A study of cisapride prescribing patterns one year before and after the regulatory action found a high prevalence of contraindicated use and no change in prescribing patterns after the regulatory action, pointing out that patient understanding of drug risks need to be improved. An FDA study analysing industry-conducted assessments of 66 medication guides by surveying patient knowledge showed that only 30% met the acceptable knowledge rate of 80% or more responders correctly answering questions about the primary risk.

In addition, FDA has started a new multidisciplinary multi-model research project to evaluate the impact of drug safety communications on zolpidem which includes warnings of next day drowsiness, driving impairment and recommendations for a lower starting dose. This approach examines prescribing trends and health outcomes and involves direct interviews with patients and physicians, including a national survey to understand how messages are disseminated in practice.

Mr. Shinobu Uzu, Pharmaceuticals and Medical Devices Agency (PMDA) Japan, presented the PMDA experience with measuring the impact of pharmacovigilance, in the context of conventional post-market surveillance. Spontaneous ADR reporting, early post-marketing phase vigilance (EPPV) and real-world use surveys are key data sources. EPPV is the early post-marketing phase of intensive monitoring where MAHs are required to provide healthcare professionals with safety information (e.g. through hospital visits, letters, fax, email or retailers) and to collect ADR information. Real world use surveys are conducted to collect safety and efficacy data of approximately 3,000 patients or special populations such as the elderly, patients with renal or hepatic disorders or other targeted ADRs under real world conditions. For intensive monitoring purposes all patients taking drugs are registered to obtain comprehensive benefit and risk information for a designated period. The limitations of conventional post-market surveillance such as underreporting of ADRs, lack of drug utilisation data to quantify risks and cost effectiveness are also being discussed. PMDA therefore launched new activities

including the Medical Information for Risk Assessment Initiative (MIHARI) which uses electronic health records to evaluate safety risks quantitatively as part of the regulatory process of drug safety assessment. One of the key findings of the MIHARI project was the evaluation of the risk of hyperlipidaemia with atypical antipsychotics which showed that olanzapine had a risk ratio of 1.5 compared with other atypical antipsychotics.

Another activity is the Medical Information Database Network (MID-NET) system which is a network of 10 hospital databases to integrate hospital records data, claims data and other outcome data remotely for quantitative risk assessment. From 2018, MID-NET will be rolled out for full scale research purposes to regulators, academia and pharmaceutical companies to address drug safety questions and for benefit-risk assessment.

Further pharmacovigilance activities include the project 'Child and Drug Information Centre' which focuses on drug use in children, leveraged by the network of paediatric medical institutions with the aim to set up safety measures for paediatric medicines and to contribute to the development of paediatric medicines.

Dr. John Patrick Stewart, Health Canada, explained Health Canada's approach to measuring the impact of pharmacovigilance and regulatory decisions. In Canada federal government programs are required to demonstrate that they meet their intended objectives and outcomes and deliver public health benefits for its citizens with a focus on key risk mitigation strategies. The results of impact measurements facilitate regulatory decision making on which activities should continue and which should be modified or stopped. The current approach to measuring impact of pharmacovigilance is retroactive rather than systematic and prospective, and distinguishing the effects of regulatory measures on health outcomes is challenging, at best a contribution can be measured as public health is a shared responsibility with many players and factors. Technological advances over the last 15 years have led to more patient centred pharmacovigilance and monitoring of real world evidence of benefits and risks of marketed products. In this context Health Canada has developed the LOGIC model[7] as a results-driven approach for health products vigilance, which defines the key programme activities and outputs and links them to direct, intermediate and ultimate higher level health outcomes. Direct outcome indicators measure how the framework is achieving the intended health outcomes (e.g. number of signal assessments resulting in regulatory action). The model links the results for each activity with the expected sequence of desired objectives, outcomes and impacts. Ultimate outcome measures look at reduced mortality and change in quality of life at population level.

Process indicators which are easier to measure and less costly and time consuming are used as proxies for direct outcome measures, including volume indicators of performance, e.g. the impact of RMPs on the ability to anticipate post-marketing safety signals before a licence is granted. During 2007 and 2015 the review of pre-approval RMPs for new drugs led to the correct identification of post approval safety concerns in 66% of cases, in 34% of cases safety concerns were not picked up during the RMP review. The events that were unpredictable prior to approval were generally idiosyncratic in nature, rare events or occurred with first in class drugs. The number of requests for additional risk minimisation activities has increased over time (i.e. 24% of all reviewed RMPs for new drugs between 2007 and 2015 include additional measures) which demonstrates that the peer-review process of RMPs is adding value to the safe and effective use of medicines. Examples of direct outcome measures include e.g. drug utilisation studies which measured the effectiveness of rosiglitazone risk minimisation showing a contribution towards the decline in overall rosiglitazone prescribing following the label change and regulatory communication in relation to the increased risk of myocardial infarction. Drug utilisation studies (e.g. number of prescriptions issued) are useful to measure impact of regulatory actions as a *contribution* but no *attribution* can be demonstrated as various players are taking action at

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[7] http://www.hc-sc.gc.ca/ahc-asc/performance/eval/evaluation-health_sante-initiative-2012-2015_longdesc1-eng.php

the same time all contributing to the overall impact on prescribing. In the example of isotretinoin, a retrospective cohort study showed that despite the implementation of a pregnancy prevention programme a residual risk of foetal malformations prevails which highlights the need to clearly define success (or failure) of risk minimisation measures, and for pregnancy prevention programmes this is still an outstanding question.

Regulators need to understand the potential unintended consequences of regulatory actions, and involving stakeholder groups in technical discussions about risk minimisation strategies helped Health Canada to amplify safety messages (using e.g. social media, pamphlets and web banners) following a signal of liver injuries with acetaminophen overuse in 2014. Prior to launch of the educational campaign a survey provided baseline understanding of Canadians' knowledge of acetaminophen containing products and their safety profile. A public opinion survey on post-market surveillance launched in 2006 has helped to understand the effectiveness of communication methods for new public health information and to develop new communication tools. In addition, comparative effectiveness studies on the clarity and readability of public advisories led to the development of a tool to reduce the health literacy burden by assessing the suitability of risk messages and communication materials.

For the future, it is recommended that we work collaboratively to put concerted international effort to establish a systematic approach, including using harmonised indicators, to measure impact of pharmacovigilance activities to maximise return on investment and deliver optimal value to our citizens.

Dr. Robert Reynolds, Pfizer Inc., shared how industry is approaching the impact of pharmacovigilance activities. The PRAC impact strategy approach provides an opportunity to go beyond product-specific impact to measuring the system impact of various data sources, analytic approaches and regulatory documents. Outcomes of interest for system evaluation might be the ability to identify new signals or to identify signals that result in label changes. The strategy also provides a useful framework for measuring the impact of innovation, including new analytic techniques and data sources whereby the ultimate pharmacovigilance system outcome measure is public health and patient safety. Regulators required industry over the last 10 years to evaluate the effectiveness of product-specific risk minimisation measures as part of EU-RMP and REMS programmes which both use similar outcomes and methodologies. For example, an 18-month REMS assessment survey of the effectiveness of the varenicline medication guide concluded that the guide was received and patients understood the potential risks but low response rates were a limitation and this methodology cannot isolate the impact of risk communication from other sources (e.g. media, medical societies etc.). Targeting the right prescribers in different national health care systems and national regulatory requests to customise evaluation tools are typical challenges industry is facing. To address some limitations of this survey methodology industry is exploring the measurement of changes in physician and patient behaviour at the population level. For example, the impact measurement of a 2010 class label change for proton pump inhibitors warning of the increased risk of bone fractures, using the Sentinel rapid analysis tools, suggested that the intended change in behaviour was effective due to a decrease in use time and lower starting doses. Another option for assessing impact at product level may be a hybrid approach where in closed healthcare systems behavioural patterns are first evaluated at the population level and then patients and physicians could be selected for surveys or interviews to better understand their decision making.

The Escher report (2014)[8] assessing the impact of the EU pharmacovigilance legislation is one of the few examples of measuring system impacts in terms of understanding whether the legislation has simplified pharmacovigilance tasks and decreased duplication. The report demonstrates that a variety of methods and data sources can be used to assess impact and the value of specific regulatory

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[8] Boon, W.P.C. et al. Improving the EU system for the marketing authorisation of medicines. Learning from regulatory practice. Published by Escher – The TI Pharma Platform for Regulatory Innovation, Leiden, Netherlands, 2014. Available at http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf

requirements for public health in relation to costs and alternative regulatory options. The report highlights opportunities to optimise RMP strategies to resolve uncertainties but also the challenges of system impact measures.

Big data analytics is an area that could be useful to better understand and evaluate innovation in pharmacovigilance. Our capacity for real time analysis of large digital data streams should enable better and faster decision making, and innovative approaches such as hypothesis-free signal detection in electronic health records can be evaluated to determine if these sources identify unexpected signals or signals earlier than those by spontaneous reporting systems. The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT)[9] project has further advanced the evaluation of electronic health records for signal detection and concluded that this approach is currently complementary to spontaneous reporting. Research showed that the use of unstructured data in electronic medical records can improve the detection of acute liver injury and identify onset of cases earlier than using coded/structured data alone. The impact framework provides an opportunity to measure the contribution of natural language processing, machine learning and other techniques applied to big data. The contribution of social media to impact research needs to be further explored as published literature suggests that social media is unlikely to be a source of medical detailed case reports due to the nature of reports and the difficulty of signal follow-up, but there may be added value in measuring patterns in aggregated rather than individual reports.

In conclusion, measuring the impact of pharmacovigilance actions is a very useful development to optimise the benefits and risks of medicines with an adaptable pharmacovigilance system. It is challenging to identify meaningful outcomes at pharmacovigilance system level but the framework can assess real world outcomes of regulatory actions to identify opportunities for improvement and to create a learning system. The framework is also an opportunity to re-allocate efforts to those measures which are proven to be most effective for public health and patient well-being.

Dr. Sabine Straus, Medicines Evaluation Board, summarised the challenges and opportunities to measuring the impact of regulatory actions from a national competent authority's perspective. Regulatory actions can take a wide range from the most frequently 'no action taken' to revocation of a marketing authorisation. Today's range of pharmacovigilance tools allows regulators to refine benefit-risk assessments and to demonstrate public health benefits of new treatments. In the EU cumulative reviews of spontaneous ADRs in periodic safety update reports (PSURs) led in about one third of the assessments to variations of marketing authorisations. GVP XVI provides guidance on how to measure the effectiveness of risk minimisation activities with process indicators providing evidence that risk minimisation has been implemented, and more challenging outcome indicators providing an overall measure of the level of risk control. A good example for the assessment of risk minimisation measures is the geographic variation of the use of rosiglitazone as a combined effect of the publication of a meta-analysis, the FDA warning and associated media coverage, demonstrating a 70% decrease in the use of rosiglitazone in the US. To distinguish the effects of press releases and DHPCs from the effect of published literature, a trend analysis of dispensing patterns in the Netherlands was performed which suggested that prescribers respond to such safety communications (i.e. interrupted time series analysis showed that one third of the DHPCs triggered a decrease in prescriptions issued). However, whether a decrease in prescribing patters is the best possible measure of success may be debatable and regulators should provide further guidance on how impact could be evaluated (i.e. objectives, target population, data sources, methods, success criteria etc.). The challenge with DHPCs is the urgency of the safety issue which requires immediate action preferably with strong and actionable recommendations to a clearly defined target group.

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[9] http://www.imi-protect.eu

The difference between process indicators (i.e. implementation, awareness or changes in behaviour) and outcome indicators (i.e. direct measures of health outcomes) is substantial. The outcome of regulatory actions is the most important aspect and surrogate endpoints should only be used if no alternatives are available and feasible as stipulated in GVP XVI. For example, the pregnancy prevention programme (PPP) for isotretinoin involves all stakeholders, i.e. prescribers, pharmacist, patients and payers. Evaluating the effectiveness of a PPP is complex and the choice of outcome to assess is challenging (e.g. no pregnancies, no babies with birth defects, full compliance with recommended contraception or full understanding of the teratogenic risk at the level of prescriber and patient). In this area research found that although an isotretinoin PPP had been implemented in the Netherlands since 1988, there are still exposed pregnancies and adverse foetal and neonatal events occurring today, raising questions on the compliance with the PPP requirements.

Another challenge to measuring the outcomes of risk minimisation is the data source, e.g. spontaneous reporting may not be the most suitable source to assess impact due to underreporting. Systematic data collection and active surveillance/sentinel sites are costly and time-intensive and may not detect rare events. Surveys may not be the most appropriate approach to assess changes in behaviour and may be biased by low response rates. Recycling existing data cannot always provide answers to relevant questions. Active data collection provides an opportunity to address specific questions but this takes time which may not be compatible with the need for speedy action. Another challenge is outcome definitions, i.e. what do regulators want to achieve and how should this be measured taking into account background incidence rates of targeted events, as an example. Electronic health record data may provide a solution but previous research in the EU has shown that additional risk minimisation measures often cannot be assessed because of vague formulation of the objectives, hence there is a need for actionable and measurable recommendations with clearly defined objectives. The evaluation of the achievement of goals and the performance of tools must be separated as they may not necessarily be linked, and also process and outcome indicators need to be distinguished as they may require different remedies. Defining thresholds of success also means that good effectiveness may not always require 100% and more is not always better.

Session 3.1: Enablers and barriers to measuring impact – patient and healthcare professional engagement (parallel session)

Prof. Patrick Brown, University of Amsterdam, opened the session with the topic "Defining engagement – awareness and perception of public health measures" with conceptual thoughts about the meaning of engagement, who is being engaged and how engagement could be measured. The literature describes various concepts for engagement, i.e. one-way communication from an authority to a broad audience, consultation of the public on a specific question and as a two-way discussion and motivation. In practice these concepts are not discreet models but occur as combinations and different types of engagement are relevant in different contexts. The most appropriate level of engagement depends on the nature of the risk which can be described as simple/linear (i.e. causes are well known), complex (i.e. multiple causal factors influence each other), uncertain (i.e. there is a high degree of residual risk) or ambiguous (i.e. lack of consensus what are acceptable levels of risk or good outcomes). In the context of medicines regulation engagement between individual stakeholders (regulators, healthcare professionals, medicine users, manufacturers and the media) may follow different dynamics and underlying conceptions. Engagement as a process becomes measurable over time (e.g. how many people) and effective engagement requires maximisation of participation through knowledge transfer, motivation and trust in the regulatory authority. The quality of the information provided and how it builds competences and confidence is an important qualitative measure for

effective engagement which has also been operationalised quantitatively in the literature[10]. Effective tools of engagement are required to maximise the transfer and processing of information. Engagement also means that various actors are included and their public values and social concerns play a key role in framing the risk which regulators need to consider. In this context the potential benefits of unstructured free-text reporting to measure engagement could be further explored. Effective engagement of professionals requires vigilant physicians who generate a suspicion and report the ADR. However, the literature describes various factors for professionals non-reporting: ignorance, diffidence, confidence, complacency and time pressure. Those barriers should be tackled through knowledge sharing and confidence building. Since engagement is hard to operationalise, surrogate measures may be applied such as *i) knowledge of regulators and reporting mechanisms, ii) overall levels of reporting, iii) measures of the quality of reporting, iv) measures of under-reporting* and *v)* trust in regulators and the reporting process.

Dr. Rachel Sobel, Pfizer Inc., and **Dr. Terri Madison**, Mapi Group, jointly presented the highlights of the ISPE white paper "Evaluating the Effectiveness of Additional Risk Minimisation Measures via Surveys in Europe: Challenges and Recommendations"[11] with a focus on how survey data can help to understand and measure engagement. Surveys are well established to measure process indicators and focus on the implementation of a risk minimisation measure and the assessment of knowledge and of clinical behaviour, but have a lower place in the evidence hierarchy due to potential selection bias. Well-designed survey studies are a reliable and rigorous method to measure stakeholder knowledge rates but current guidance does not stipulate thresholds of knowledge indicating success or failure (the 80% threshold widely used is empiric and not validated). In addition, implementing survey studies in the EU is challenging due to classification as post-authorisation study (PASS) in line with GVP which leads to lengthy regulatory and ethics submissions to meet regional and institutional requirements which is barrier for timely feed-back. Country specific limitations could challenge the representativeness of a survey and the PASS classification, which varies across countries, does not necessarily result in greater data quality. Recruitment is another challenge limiting a representative sampling frame and the PASS designation is also a barrier to incentivising. Due to privacy restrictions in several EU countries contact information held by MAHs may not be used to recruit for a survey. These challenges have major implications on the feasibility to conduct a pan-European survey in a timely, efficient and cost-effective manner and introduce the potential for selection and information bias jeopardising the generalisability of the survey results.

The ISPE recommendations are aimed to better enable the conduct of survey studies. In GVP it should be clarified that survey studies of knowledge of risk and risk minimisation behaviour to evaluate process indicators do not fall under the PASS category and the classification of behavioural endpoints in GVP XVI and CIOMS IX should be aligned. GVP XVI should be updated with robust survey methodologies and analytical approaches to improve scientific rigor and avoid the categorisation of 'market research'. Promoting a consistent centralised process for the conduct of surveys in multiple EU countries without the need for country-specific approvals would reduce many operational challenges of surveys and delays of public health impacts. It is further recommended to clarify the conditions when routine risk minimisation measures require effectiveness assessments. MAHs should also specify which social science evaluation framework they are using to measure the effectiveness of additional risk minimisation measures.

Mr. Marin Banovac, European Medicines Agency, presented the results of a study describing patient reporting in EudraVigilance and discussed if reporting could be a possible measure of patient engagement. The study compared patient and healthcare professional spontaneous reporting of ADRs to EudraVigilance before and after the implementation of the EU pharmacovigilance legislation in four

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[10] Figueiras A, Herdeiro M and Polonia J. An educational intervention to improve physician reporting of adverse drug reactions: A cluster-randomized controlled trial. JAMA 2006; 296:1086-1093.
[11] http://pharmacoepi.org/pub/f46953df-de69-31e7-8f74-725bd7fa685f

primary reporter groups, i.e. patient, healthcare professional, patient with healthcare professional or pharmacist as co-reporter, and lawyer. The results indicated that the total number of annual reports increased in all four groups but tripled for patients between 2009 and 2015. The proportion of patient reports in EudraVigilance increased from 9% to 15% for patients as primary reporter. In the EEA patient reports per million inhabitants were highest in the Netherlands with 706 reports per million between July 2014 and June 2015. The results also show an increase of reports of serious cases from patients after changes to the legislation compared with before, but this needs to be interpreted with caution given the transitional reporting rules for non-serious cases. The study results showed that reports from patients and healthcare professionals share the top three most frequently reported System Organ Classes (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA) and 13 of the 20 most frequently reported reactions coded with MedDRA Preferred Terms (PT) in patient reports were also among the top 20 most frequently reported reactions reported by healthcare professionals, indicating that patients report similar medical conditions. As regards the differences, patients tend to report more than healthcare professionals the reactions affecting their quality of life and less laboratory results in line with findings of previous studies on patient reporting. The results also showed that for drugs given for genitourinary, hormonal and/or reproductive disorders patients are more likely to report ADRs than healthcare professionals.

In summary, overall patient reporting in EudraVigilance increased after the implementation of the EU pharmacovigilance legislation. Whether the quantification of patient ADR reporting can be correlated with patient engagement remains debatable but the results show that the legislation has driven patient empowerment as intended.

Session 3.2: From regulatory outputs to health outcomes (parallel session)

Prof. Stephen Evans, London School of Hygiene and Tropical Medicine, started this session with a presentation on methods to go from process outcomes to health outcomes e.g. by using surrogate measures and interrupted time series (ITS) regression analyses. To examine whether the ITS method was adequate to estimate impact of regulatory actions the effect of media coverage on statin prescribing was studied, which had caused major headlines in the UK between October 2013 and March 2014 due to side effects. Regulatory actions and media effects are difficult if not impossible to disentangle and Matthews et al. (2016)[12] examined initiation and stopping of statin prescriptions in the Clinical Practice Research Datalink (CPRD) database between January 2011 and April 2015. The primary analysis modelled changes in the proportion of patients initiating and stopping statin therapy for *primary* and *secondary* prevention before and after the media coverage. There was an increase of the proportion of patients initiating a statin therapy for *primary* prevention between Jan 2011 and Jan 2013 (first time prescription in patients with risk factors such as high blood pressure, high cholesterol and high age). During the period of interest (Oct 2013 – Mar 2014) prescriptions fell and after the media coverage moderately increased again with an odds ratio of 0.99. For *secondary* prevention the same analysis showed a fall over the whole period with a slightly bigger fall during the period of interest and increase to previous levels after the media coverage (odds ratio = 1.04). The analysis also showed constant statin cessation rates for *primary* prevention which remained the same during the period of interest but did significantly increase in the period after the media coverage with an odds ratio of 1.11. A similar result was shown for cessation rates for *secondary* prevention. Another analysis showed that the effect of media attention decayed fairly quickly after a period of 6 months. Modelling the public health impact showed that 218,971 excess patients stopped statins following the 6 month after the media coverage, and estimating that 20% of patients had a 10-year cardiovascular disease (CVD) risk and statins reduce the risk of CVD by 19%, at least 2,173 excess CVD events will occur

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[12] Matthews A. et al., Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ 2016; 353:i3283.

within 10 subsequent years. This figure also accounts for 49% of patients that would have stopped statin therapy regardless of media coverage and 66% of patients that stopped statins for other reasons than side effects but would restart their prescription in the same period. These data need to be interpreted with caution given the vast numbers of assumptions included in the model, but the results demonstrate clearly the impact of media attention on regulatory actions. The methodological features and analytical issues of ITS have been further described by Bhaskaran et al. (2013)[13].

Dr. Maia Uusküla, State Agency of Medicines, presented the results of study of liver function monitoring in patients receiving agomelatine. The risk of liver injury is known since the authorisation of agomelatine in 2009 with a requirement for liver function monitoring in the SmPC, but cases of severe liver toxicity were reported despite DHPCs in 2012 and 2013. In 2014, a physician's guide with a liver monitoring scheme and a patient booklet were implemented. In the Estonian Health Insurance Fund (EHIF) database all purchased agomelatine prescriptions issued to new users in the period January 2012 to May 2016 were identified and the data analysed to determine whether these patients received liver function tests at initiation or during treatment by comparing the test date with the date of first purchase or subsequent purchase (15 or 30 days prior to purchase). During the study period 5,630 new users were prescribed agomelatine (17,377 prescriptions issued) for depression (31%), anxiety disorder (21%) and recurrent depressive disorder (17%) in an age range of 4 to 96 years, although it is only approved in 18 – 75 year old adults. On average 3.1 prescriptions per patient were issued and 1.3 packages per prescription for an average duration of 4 months. During the study period liver function tests had been performed on average 3.8 times per patient, but *at initiation* only 984 (17%) patients were tested 15 days before treatment initiation, and 1,267 (23%) patients 30 days before treatment. *During* treatment the numbers were slightly higher but only 42 (4%) of patients were tested according to the SmPC liver monitoring scheme. A time trend analysis showed that the proportion of patients with a liver function test at least once before or during treatment was stable between 40 - 50% despite increasing numbers of new users and additional risk minimisation measures. The results concluded that adherence to the liver function testing scheme was poor and that further regulatory action and communication may be warranted. Methodological challenges of this retrospective, cross-sectional drug utilisation study include the non-specificity of liver tests recorded in the EHIF database, the lack of test results and problems with defining patient characteristics based on insurance claims. Advantages of this methodology include linkage with prescription data, diagnosis and healthcare data via the patient ID which allows analysis of concomitantly used medicines, laboratory tests, the indication and whether prescribing and dispensing restrictions were followed.

Prof. Saad Shakir, Drug Safety Research Unit, introduced the topic "modelling methods to estimate the public health impact of regulatory decisions", based on a research proposal to measure the impact of product withdrawals and other major pharmacovigilance actions on public health burden. A literature research of the evidence supporting product withdrawals in the UK and the US between 1999 and 2001 showed that most withdrawals relied on spontaneous reporting and in very few cases interventional or observational studies provided additional evidence. When the study was repeated for product withdrawals during 2002 and 2011 a shift could be seen with two thirds of withdrawals citing evidence from observational studies in addition to spontaneous reporting to support regulatory decisions. Whether a shift towards more robust evidence improved public health in terms of better regulatory decisions leading to reduced mortality and morbidity from ADRs is unclear. A study is proposed to examine the public health impact of this shift quantitatively and to investigate the effects on public health burden of these decisions, measured by the effects on mortality and serious morbidity. The study will use predictive modelling methods based on empirical utilisation data of respective products and describe the evidence used to support withdrawals in the EU between 1999 and 2002, 2002 and

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[13] Bhaskaran K. et al. Time series regression studies in environmental epidemiology. Int J Epidemiol 2013; 42:1187-1195.

2011, and after 2012. Quantitative description of the data sources upon which the decisions were based will be provided (where possible) and descriptive statistics of safety and drug utilisation data. The key point of this analysis will be to link the findings on relative risks and attributable risks with usage data (from IMS, THIN or CPRD) to estimate how much morbidity and mortality was prevented as a result of conducting these studies, and to measure the effect on public health burden. Also sensitivity analysis to examine the public health impact at earlier time points will be applied to understand at what time sufficient evidence was available to take a regulatory decision, and then to model based on the reduction that happened after the regulatory decision what were the missed opportunities by way of reducing morbidity and mortality had this decision happened earlier. The research project will initially focus on product withdrawals, and later extended to restrictions, contraindications and major label changes.

Session 3.3: Measures of impact of pharmacovigilance processes (parallel session)

Dr. Judith Sanabria, University Hospital of Malaga, introduced the "Challenges of measuring impact of new pharmacovigilance processes". Based on the example of drug-induced liver injury (DILI), the possibility to focus measures of impact on ADRs which require more attention than others was explored. The classification into type A for predictable, dose-related adverse reactions with high incidence and morbidity rates and type B reactions for unpredictable, without clear dose-relation, low incidence and high morbidity rates was considered. DILI are typically type B reactions responsible for >10% of all acute liver failure cases and one of the most frequent reasons for post-marketing regulatory actions which vary from label changes to product withdrawals. Challenges in measuring the impact of pharmacovigilance processes related to DILI start with the risk identification in terms of diagnosis, causality assessment, lack of predictive models, lack of systematic safety data capture and analysis, lack of harmonised case definitions, etc. which lead to significant variation of SmPC information. Guidance on protocols for the systematic assessment of DILI cases including clinical trial data may improve risk identification with harmonised terminologies and standardised electronic data capture systems. Underreporting, the lack of drug prescription and dispensing data, and the time gap between risk identification and regulatory actions are a challenges for timely B/R evaluation. The combination of large clinical trial data sets, use of validated biomarkers and personalised medicine approaches may provide potential solutions to improve risk quantification through well designed studies. The Spanish DILI registry was established to monitor liver safety and products could be withdrawn in relative short timeframes, which underpins the potential of registries to identify signals more timely and efficiently. Measures of the impact of DILI registries on regulatory decision making could focus on the time gap between signal identification and regulatory action and ultimately whether DILI related product withdrawals decrease over time.

Dr. Nawab Qizilbash, Oxon Epidemiology, presented the preliminary results of a review of ten survey studies to evaluate the effectiveness of additional risk minimisation measures published in the EU PAS Register with a study report. Additional data sources included public PRAC plenary minutes, study reports from pharmaceutical industry and PRAC assessment reports obtained through EMA's access to documents policy. Independent data extraction methods were applied to those materials. The review included 9 active substances with different indications and safety concerns, and educational materials in 8 cases. In 9 studies the target audience were healthcare professionals and in one study patients. Nine surveys were conducted as cross-sectional one-way study in more than 5 EU countries and 5 surveys used a random sampling frame. Process measures included receipt rates of the materials, knowledge of safety concerns, usage and regulatory consequences. There was a great degree of variability in the definitions and terminologies used to express participation e.g. as eligibility, response, completion or cooperation rates and only a few studies provided flow charts. The pooled estimate for the participation response rate defined as *eligible* versus *completed* responses over the whole sample

was over 95%, but there was heterogeneity amongst individual studies. Using instead the definition *completers* versus *target population* for the response rate provided a different pooled estimate (below 5%) which demonstrates the potential for bias for other process measures which depend on response rates. Preliminary results of 6 studies showed a pooled receipt rate of 47% but given the above caveats the analysis should focus on forest plots and not pooled estimates due to the high degree of variation. There also seemed to be a correlation between receipt and response rates but the range of response rates was low and this analysis only included 4 data points, hence more data needs to be included for conclusive findings. In summary, this limited preliminary analysis showed immense variation in the conduct and reporting of survey study results in terms of definition of participation rates, sampling, country selection and validation of questionnaires which impact on the results. Most study designs lack clinical and safety related outcomes and focus on process outcomes without clear criteria to assess success or failure. There is a need for additional guidance on the conduct and reporting of survey studies with standardised terminologies and presentation of results.

Dr. Amie Goulbourne, Biogen, introduced the topic "Measuring time from identification of a new risk to regulatory action with focus on signalling tools and processes". The time between identifying a new risk and regulatory actions (e.g. safety communication) is a measure for impact of pharmacovigilance processes. Collecting and analysing the data to create safety communications however takes time and lessons are learnt by all involved parties as more data is generated and reviewed in an iterative process. Based on the example of Tysabri® it was demonstrated how the type and quality of data for PML cases has evolved since 2005. With implementation of a PML database and prescriber education the number of cases increased along with the quality of the information which allowed for the identification of 3 key risk factors (time on treatment, prior immunosuppression and presence of anti-JCV antibodies) in 2010. In 2012, a risk algorithm to identify patients which benefit most was created and risk factors further refined in 2016. Compared to 2006, when just a simple risk rate was included in the SmPC, collecting and reviewing different types of data and applying learning to improve data collection and analysis by educating patients and prescribers delivered a detailed algorithm to help selecting the right patient for treatment. The evaluation of safety data and signal identification is often challenged by poor quality of early post-marketing data limiting the assessment of initial cases. Significant investment in data collection schemes not necessarily provides meaningful data for critical medical decisions which is also due to unclear roles and responsibilities. Solutions to generate more meaningful data focus on experience and educational outreach to reporters, use of statistical and visualisation tools to improve efficiency in detecting trends, use of novel technologies to support data collection and analysis, and the combination of alternative data sources (e.g. laboratory data, epidemiological studies, clinical trials, spontaneous reporting, claims data etc.). To increase speed and accuracy in signal detection and risk assessment, processes with clear roles and responsibilities for effective decision making are needed which also address different regional data requirements. The lessons MAHs, healthcare professionals and regulators learnt from the Tysabri® example show that data collection quality can be significantly improved over time through the proposed solutions.

Prof. Eric van Ganse, Pharmacoepidemiology Claude-Bernard University and Croix Rousse Hospital Lyon, introduced the study "The risks of asthma therapy as assessed from real-life data: ASTRO-LAB & SNIIRAM". The ASTRO-LAB project is assessing the benefit/risk ratio of long-acting beta-agonists (LABAs) in asthma in routine care by combining healthcare databases e.g. from the French NHS claims database of reimbursed interventions (SNIIRAM) and direct patient follow-up. Studies conducted in the US did not find any increased risks of LABAs when combined with inhaled corticosteroids (ICS) in fixed-dose combinations, whereas in the EU the ASTRO-LAB study was based on the hypothesis of a differential use of LABAs and ICS outside a fixed combination and patients were closely monitored for the therapy used and the occurrence of adverse outcomes (e.g. exacerbation of asthma). The results showed a signal of increased adverse events when LABAs are used as monotherapy or in free combination with ICS in contrast to fixed-dose combinations. The US results were confirmed and no

signal was identified, supporting the differential use hypothesis. Confirmatory studies based on SNIIRAM identified two use patterns of asthma therapy amongst patients at risk of adverse outcomes: *i)* LABA use unbalanced by co-therapy with ICS ("differential use") and *ii)* high use of short acting beta agonist (SABA). Looking retrospectively at how asthma therapy was used in patients before they were admitted to hospital to treat critical conditions such as asthma exacerbation based on SNIIRAM data identified three clusters of patients *i)* with low exposure to LABA, ICS or fixed-dose combinations (classical patient group stopping asthma therapy as soon as they can), *ii)* with high use of fixed-dose combinations and *iii)* with higher use of LABA than ICS (differential use). The study results show that there is an inappropriate pattern of use of asthma therapy in France (and UK where the study was also conducted) which might be related to prescribing behaviour of healthcare professionals or patient use, but direct LABA toxicity was not suggested. Additional ancillary studies using SNIIRAM data showed a high prevalence of inappropriate use of asthma therapy and a correlation between LABA/ICS differential use and hospital admissions. The impact of regulatory interventions in 2010 by EMA requesting a safety study and 2011 by FDA issuing safety alerts for LABAs is reflected in a drop in sales figures (based on SNIIRAM data).

In summary, the pharmacovigilance activities for LABAs in asthma therapy could serve as a model for impact evaluation. The ASTRO-LAB study supported the absence of toxicity and emphasised the need to prioritise prevention of inappropriate use patterns which can be identified by targeted, automated screening of SNIIRAM data. Repeated SNIIRAM surveys may be used to assess the impact of such activities.

Session 4: Reports from breakout sessions: gaps and observations

Dr. Martin Huber, Federal Institute for Drugs and Medical Devices, summarised the findings from breakout session 3.1. "Enablers and barriers to measuring impact – patient and healthcare professional engagement" based on the case examples presented:

- Prerequisites for patient and healthcare professional participation in impact measurement are initiatives to raise awareness and trust in medicines regulation beyond the value of reporting but also to increase confidence that their contribution to impact assessment (e.g. through participation in studies) makes a difference;

- Industry initiatives seem to be a barrier for engagement whereas regulators are considered a better trusted source for information on the benefits and risks of medicines. There is clear need for trust building measures as otherwise communication pathways may need to be adjusted, taking into account the heterogeneity of risk communication and health literacy of the target population;

- There is limited understanding of patients' and healthcare professionals' preferences, how they perceive public health measures and value risks before regulatory measures are implemented;

- Patients need to be better educated to enable them to take more responsibility for their health, but that requires a change in attitude and competences to manage this cultural change, e.g. through closer collaboration with patient communities to establish patient needs and to improve health literacy, and early involvement in the regulatory decision making process and the choice of communication tools;

- EU regulatory communication should focus on the *proper* use of medicines with a shared responsibility of all stakeholders to demonstrate both the benefits and the risk for patients. Tools

for regulatory benefit-risk communication aimed at sharing information, changing beliefs or behaviours have been reviewed by Way et al. (2017)[14];

- Survey studies' validity and reliability are undermined by low participation rates, operational challenges (e.g. selection bias, generic product risk minimisation identification) and complex regulatory requirements. There is a need for clarification how national regulators categorise survey studies and assess results in the context of GVP; alternative qualitative approaches such as focus-groups and interviews which provide similar meaningful results may be considered on a case-by-case basis;

- To measure engagement quantitative research methods could be enhanced through triangulation techniques (i.e. combining survey data with behavioural outcomes and drug utilisation data) to account for multiple dimensions of engagement;

- Promotion of universal tools for patient reporting (e.g. globally standardised forms) is needed;

Dr. Daniel Morales, European Medicines Agency, summarised the findings from breakout session 3.2. "From regulatory outputs to health outcomes" based on the case examples presented:

- Predictive modelling methods to estimate the public health impact of regulatory actions require a collaborative approach to determine the right design for the right research question with focus on outcome measures (or process indicators as surrogates where appropriate).

- Interrupted time series (ITS) regression can be applied for modelling health outcomes of regulatory actions. As with all modelling approaches it is important to ensure the key modelling assumptions are met (e.g. trends before the intervention continue to be true after the intervention of interest and data points are independent) and that the context of clinical practice is well understood in terms of *clear intervention dates* (e.g. regulatory procedures end with a European Commission Decision date after which label changes are implemented in Member States but the actual date locally may be difficult to determine), measuring *events related to intended health outcomes* (e.g. modelling events with long onset time versus acute outcomes), *competing prescribing interventions* (e.g. impact of specific products on wider health outcomes), *time-varying confounding* (e.g. multiple events taking place over time that impact on causal interpretation of time series data related to changes to clinical guidelines, media impact and other forms of communication) and *acceptable levels of change*. Also the limitations of ecological studies need to be considered.

- The effect of combining exposure data from different sources and countries to increase power and generalisability depends on the variation across healthcare systems and the outcome of interest ('soft versus hard outcomes') which needs to be clearly defined in the context of the intervention.

- Methods to evaluate impact need to account for impacts in subpopulations (through patient characteristics) to detect changes in health outcomes depending on the different baseline incidence of the outcome of interest. This may be incorporated in the design of such studies. Negative controls can help to infer if associated changes in health outcomes are related to the regulatory action or other factors such as co-prescribing.

- Qualitative studies and surveys studies are useful to fully understand the effectiveness of risk minimisation and the reasons why regulatory actions did or not achieve their intended impact.

- A core set of research initiatives to study the effect of safety communications on physician and patient decision making has been described by Kesselheim et al. (2015)[15] which combines the

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[14] Way D. et al. Pharmaceutical benefit-risk communication tools: a review of the literature. Drug Saf 2017; 40:15-36.
[15] Kesselheim A. et al. Methodological Approaches to Evaluate the Impact of FDA Drug Safety Communications. Drug Saf 2015; 38:565–575.

analysis of prescribing and related health outcome trends, direct interviews of patients and physicians, national survey of patients, and quantitative and qualitative reviews of FDA risk communications in social and traditional media.

Prof. Marieke De Bruin, University of Copenhagen, summarised the findings from breakout session 3.3. "Measures of impact of pharmacovigilance processes" based on the case examples presented:

- The impact of signal detection processes could be measured by the time lag between signal identification and regulatory action for certain types of adverse reactions (e.g. type B adverse reactions such as drug-induced liver injury); challenges related to risk analysis and quantification could be addressed by guidance on protocols for systematic assessment of signals, consensus on the level of evidence including from clinical trials and electronic healthcare data and standardised electronic data capture systems.

- Solutions to reduce the time gap between identification of new risks and regulatory actions include

  - improving quality of safety data through educating reporters,

  - using data base technology to support data collection and statistical analysis,

  - using visualisation tools to improve efficiency in detecting trends,

  - combining alternative data sources (e.g. laboratory data, epidemiological studies, clinical trials, spontaneous reporting, claims data etc.) and

  - a single assessment process with clear roles and responsibilities.

- Survey studies to evaluate the effectiveness of risk minimisation measures based on process outcomes require clear criteria for success, good participation rates, sampling, geographical spread and validation of questionnaires; specific guidance on the design, conduct and standardised reporting of results of survey studies may help to increase their value.

- Real time monitoring of drug usage in population-based electronic health records is a key activity to identify inappropriate patterns of use of therapy, and a tool to detect signals and to measure healthcare professionals' prescribing behaviour and patients' use of medicines; for impact research such models could help to prioritise prevention strategies for inappropriate use of medicines.

- The selection of pharmacovigilance processes for impact evaluation may focus on activities where the legislation requires collection of data on their effectiveness such as risk management, signal detection and PASS; however, the current regulatory system is not set up to provide comprehensive data on these processes (e.g. number of requested RMPs, compliance with RMP/PASS timelines, regulatory consequences of PASS results, number of new signals generated, number of risk communications by regulators, estimates of public health impacts, number of drug withdrawals etc.). Alternatively, a standard model of product delivery where different processes have different goals and methods (e.g. exchange of information, change of peoples' beliefs and behaviours, reduction in prescriptions etc.) could be applied or there is focus on the processes which are most burdensome for healthcare systems, in resource and economic terms, may have the highest public health impact, or are those which experts in the field identify as problematic.

- There is need for a general framework for impact evaluation of pharmacovigilance which combines product-specific regulatory measures with the disease-specific aspects of the healthcare system to be able to evaluate both intended and unintended effects of regulatory actions.

- The evaluation of the PASS process should focus on feasibility (i.e. sample size, data quality, generalisability), protocol quality (i.e. to ensure uncertainty about a risk can be reduced) and

differentiation between PASS to investigate identified and potential risks from PASS evaluating the effectiveness of risk minimisation measures.

- The evaluation of reporting processes should focus the use of alternative data sources (e.g. electronic healthcare records and health insurance claims data), importance of population surveillance and differentiation between mechanisms behind spontaneous and solicited reporting.

Session 5: Way forward and next steps

Dr. Agnes Kant, Netherlands Pharmacovigilance Centre Lareb, elaborated on the question "How can researchers contribute to measuring impact"? The overall aim of pharmacovigilance is to reduce harm by more appropriate use of medicines, therefore considerations about which pharmacovigilance activities and outcomes should be measured need to take into account that *i*) the effect of pharmacovigilance follows different pathways and measuring the outcomes of each pathway in isolation is challenging because pharmacovigilance activities are intertwined and often complementary, *ii*) not every aspect of pharmacovigilance (e.g. trust) can be measured and *iii*) health outcomes may be influenced by other external factors (e.g. social or economic). A simple scheme of pathways originates from data which generates knowledge that affects the behaviour of patients and healthcare providers through regulatory actions, guidance and recommendations, which all reciprocate on how medicines are used and in consequence impact on public health. One possible approach is to focus only on identified risks with high public health burden and potential for reducing harm, e.g. through suspension/withdrawal of a medicine, restriction of the indication, patient monitoring scheme, pregnancy prevention programme or additional risk minimisation measures. Although it is preferable to measure the reduction of harm as ultimate outcome, this will not always be possible. Measuring the effect on more appropriate use of medicines might be a better indicator, depending on the intended target (e.g. less use, different patient group, etc.). Because the outcomes of identified risks are based on pharmacovigilance knowledge, the level of harm reduction may be predictable. As an example, the literature was reviewed for measures of the effects of EMA recommendations to manage the risk of cardiac valvulopathy with ergot-derived dopamine receptor agonists in 2008 through a decrease of the maximum dose and echocardiography monitoring before and during therapy. The health outcomes of interest would be a reduction of cardiac valvulopathy in Parkinson patients. In the Dutch national register of drug use (GIP) a substantial decrease of use in the Netherlands was seen after the regulatory intervention, whereas published literature showed that in Japan no immediate decrease in use occurred but three years later. Patient follow-up and echocardiographic checks were performed, but only at treatment initiation. However, none of the studies could demonstrate a reduction in the incidence of cardiac valvulopathy in Parkinson patients as none of the included patients has this outcome. Another observation was the manifestation of a drop in pergolide use before the regulatory intervention. This example demonstrates the complex nature of measuring the impact of pharmacovigilance activities and more work is needed to make recommendations and develop methods for predictive modelling of health outcomes.

Dr. Elisa Ferrer, EURORDIS-Rare Diseases Europe, discussed opportunities for patients and caregivers to contribute to generate data on behavioural changes. EU legislation has strengthened patient reporting and since 2012 the number of patient reported ADRs has been steadily increasing. The added value is a contribution to identify new safety signals not identified otherwise, more detailed case information (e.g. regarding impact on daily life) and the range of issues reported (i.e. including quality issues and medication errors) which complement healthcare professional reporting. To protect patients from harm, pharmacovigilance aims to increase patients' knowledge of risks and risk minimisation measures, provided the safety information is understandable, patient organisations are risk aware and patients adhere to the safety recommendations. Today patients tend to consult the internet, healthcare professionals or patient organisations on medicines' safety with all the possible

barriers in terms of reliability and lack of time, resources or trust which may jeopardise effective communication. The consultation of patients and consumers organisations in SCOPE Joint Action work package 6 on risk communication[16] showed for example that healthcare professionals are the most trusted source of information, but patients are not familiar with educational materials and how the regulatory system works, nor do they use national competent authorities' (NCA) websites as a source of safety information. In addition, two-way mobile technologies (e.g. Web-RADR) for reporting ADRs and receiving targeted safety information are likely to change current behaviours on how patients are informed about risks and risk minimisation measures. Patient organisations can contribute to generate impact relevant data through quantitative and qualitative data collection methods which enrol patients and their families via surveys, focus groups or individual interviews to provide first-hand feed-back on the level of risk knowledge, how medicines are used under real-life conditions and to identify the most effective communication pathways. Patient behaviours can be changed through engagement in pharmacovigilance activities within their own organisations, but also in collaborative projects with regulatory authorities at EU level (e.g. through public hearings at EMA, publication of RMP summaries, scientific advice for PASS, pre-authorisation advice on RMPs, etc.) and at national level (e.g. online reporting tools with direct NCA feed-back) to influence regulatory decision making, but this dialogue needs to be fluent and requires knowledge of the regulatory system. Capacity-building programmes are essential for patients to successfully contribute to these activities for a better and safer use of medicines.

Mr. Jamie Wilkinson, Pharmaceutical Group of the European Union, spoke about how healthcare professionals can contribute to generate data on behavioural changes. A topic group on risk minimisation measures within the EMA's Healthcare Professionals' Working Party was given the mandate *i*) to discuss experience in collaboration with healthcare professionals and patients for the development, implementation and adherence to risk minimisation measures, *ii*) to facilitate input into feasibility, proportionality and effectiveness evaluation of risk minimisation measures and *iii*) to discuss how to better inform healthcare professionals about ongoing post-authorisation activities at EU regulatory network level. Based on four concrete case studies with additional risk minimisation measures (i.e. sodium valproate, high strength insulins, bisphosphonates/denosumab and fentanyl patches) a multidisciplinary survey of European healthcare professionals was conducted to explore the barriers and facilitators to the implementation of and adherence to selected risk minimisation measures using tailored, closed questionnaires. The questions focused on how existing risk minimisation measures could be optimised in terms of proportionality, feasibility and unintended consequences. The analysis of responses revealed several areas for improvement (e.g. timely delivery of information when and where the medicine is used etc.) and highlighted practical problems such as supply issues of educational materials, information overload, unclear checklists and lack of access to medical records to verify patient information. The survey also highlighted opportunities such as learning from the experiences of nurses and pharmacists in implementing risk minimisation measures, new technologies for instant access to information, and ensuring that the correct tools and media are used. Communication should be targeted to the audience with appropriate tools and media, including peer-reviewed journals and professional events. Healthcare professionals should be encouraged to integrate elements of risk minimisation into institutional protocols, clinical guidelines and professional education programmes (e.g. continuing education and professional development). Implementing behavioural changes in clinical practice can be facilitated by multi-professional collaborations established in several Member States (e.g. GP-pharmacist quality circles, professional audit in practice, error process databases etc.) and access to shared electronic health records.

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[16] http://www.scopejointaction.eu/_assets/files/7.-SCOPE-JA-Patient-and-Consumer-Organisation-Consultation-2016-06-16(5).pdf

Dr. David Lewis, Novartis, deputising for Dr. Vicki Edwards, Abbvie, presented on behalf of EFPIA concerning how the pharmaceutical industry can contribute to measuring impact. Pharmaceutical industry supports outcome-driven, sustainable healthcare systems which provide patients with equal and early access to the best and safest medicines. The initiative to measuring the impact of pharmacovigilance activities is a key step to develop a road-map for impact assessment with clear success factors, data gathering requirements and methodologies. Multi-stakeholder sharing of data on the performance and quality of pharmacovigilance activities generated throughout the product-life cycle management (e.g. DSURs, PSURs, RMPs etc.) could be used where appropriate to set benchmarks. MAHs are required to submit data on the effectiveness of risk minimisation to regulators which provides an opportunity to share information within therapeutic areas to collate and aggregate effectiveness data across key safety themes (e.g. by a third party) and to identify areas where further data collection is needed. On the other hand risk minimisation measures are frequently replicated (e.g. through generic competition), materials are not standardised, and patients often receive the same material from multiple sources. The commitment to contribute and share existing data for impact research in a transparent way and to collaborate with regulators will help to generate consistent evidence and identify key areas for improvement in terms of timeliness of pharmacovigilance processes and delivery of decision-relevant data. Therefore regulators should encourage collaboration across companies in situations where non-competitive safety information is under discussion.

To support the shift in pharmacovigilance towards communicating benefits and risks, industry can contribute qualitative and quantitative evidence whether this shift had a positive impact or which information may be missing to determine whether the impact has been positive (e.g. comparison across disease areas, product withdrawals due to information gaps etc.). In the US, initiatives looking into the standardisation of risk evaluation and mitigation strategies (REMS) point in the right direction, i.e. a REMS may be completed when evidence shows that the intended outcomes has been achieved.

In the EU however, risk management plans limited to routine measures are frequently kept ongoing whereas many products with well-known severe or serious ADRs (e.g. warfarin, diuretics) do not have a risk management system in place. Survey data on patients and healthcare professionals concerns or misunderstandings in relation to risk minimisation measures are vital to build trust but such efforts need to be coordinated to avoid multiplicity which would discourage participation.

In summary, industry welcomes the opportunity to contribute to the design and robust methodology required for impact studies given the experience with patient support programmes, drug utilisation studies, registries and access to respective data sources which allow modelling of health outcomes. The quality system emphasised by the pharmacovigilance legislation also provides an opportunity to share best practice, e.g. based on the findings from pharmacovigilance inspections.

Dr. Xavier Kurz, European Medicines Agency, deputising for Dr. Julie Williams, Medicines and Healthcare products Regulatory Agency, presented collaborative initiatives of the EU regulatory network for pharmacovigilance system impact. One of the key aims of the EU pharmacovigilance legislation is robust and timely decision making and the four pillars of the PRAC impact strategy therefore focus on the effectiveness of targeted product-specific risk minimisation activities recommended by PRAC and the lessons learnt to inform future decision making. Evaluating the effectiveness of pharmacovigilance processes on the other hand allows for continuous improvement and development of the pharmacovigilance system and the identification of enablers and barriers to understand how effectiveness could be increased. An important milestone for pharmacovigilance impact assessment was the publication of the European Commission's three years report quantifying the main activity areas such as RMPs, signals, PSURs, PASS and safety referrals which demonstrated that current pharmacovigilance processes have had a useful impact (e.g. that 52% of the signals evaluated by PRAC led to product information updates, 26 of 31 safety referrals led to variation of the marketing authorisation). Whilst studies to assess the impact of regulatory action are conducted at European level, it is understandable that national concern and public interest are often the drivers for

initiatives and studies undertaken at Member State level. However, study protocols, methods and results from these national initiatives are not consistently shared despite available tools such as the EU PAS Register. An example for collaborative work at EU level to evaluate the effectiveness of risk minimisation measures implemented after a safety referral was the development of a common protocol to study utilisation of codeine in electronic health records databases (BIFAP, CPRD and IMS Disease Analyser) of four different countries. In another example changes in prescribing trends of combined hormonal contraceptives, switching tendencies and patient risk factors related to venous thromboembolism were investigated following the restrictions implemented after a referral in 2013. Lessons from such collaboration are highly relevant for the impact work in context of the PRAC strategy. PRAC has developed a set of criteria to prioritise topics for collaborative impact research based on aspects of *public health importance* (i.e. nature and severity of the risk, magnitude of the risk, public concern), *impact on clinical practice* (extent of the regulatory interventions, impact on clinical and/or patient behaviour, impact on the use of product(s) and whether *decision relevant data* can be generated (i.e. is the topic amenable to be studied, are there suitable data sources and does the study fill gaps in knowledge in addition to studies performed by industry and academia). These criteria are being pilot tested and systematically applied to urgent EU referral procedures, other referrals and signals where changes to the product information and/or RMP are recommended by PRAC. To move forward the strategy emphasises EU regulatory network collaboration to continuously improve pharmacovigilance processes and to measure the impact of key regulatory actions through studies that generate data beyond that which MAHs provide in context of risk management planning and better support regulatory decisions.

Summary of recommendations

The objective of this workshop was to exchange ideas, gain knowledge and brainstorm how all stakeholders of pharmacovigilance can contribute to measuring the impact of pharmacovigilance activities. At the same time the impact strategy approach was tested and a number of proposals and recommendations were made to streamline ongoing initiatives from regulators, academia and industry at national and international level. In several panel discussions the participants agreed that there is clear need to measure the impact of pharmacovigilance activities based on evidence to be able to focus resources to where a difference in the current system's capability to protect public health can be made.

The key pillars of impact evaluation are robust scientific methodologies, a sustainable framework for the generation of decision-relevant data integrated in regulatory procedures, timely delivery of results and clear roles and responsibilities. Practical challenges are the many external factors (e.g. different national healthcare systems) which influence the impact of regulatory measures taken at EU level.

As a way forward a modified strategy for a more systematic public health approach which could help to determine if regulatory actions are actually affecting patient outcomes and enable regulators to change decision making in the future, was discussed. Such an approach requires closer collaboration and synergies to be leveraged amongst all stakeholders of pharmacovigilance. Pharmaceutical industry expressed their commitment to contribute and share existing data relevant for impact research and to collaborate with regulators, patient communities and healthcare professional organisations, and academia to generate the evidence needed to measure the impact of pharmacovigilance.

The Agency in collaboration with the EU regulatory network will focus on a coordinating role to progress pharmacovigilance impact research at EU and Member State level, taking into consideration the opportunities raised during the workshop which concluded with the following recommendations:

Impact research should follow the **guiding principles** of:

- Clarity of language/ terminology and a clear framework for actions and activities

- Robust science (research programme, preparatory research)

- Focus on benefit risk impact and public health outcomes

- Consideration of the therapeutic/clinical context

- Consideration of unintended consequences of regulatory decisions

- Stakeholder and partner collaboration with a key role of patients and healthcare professionals

The following **key areas for actions** are proposed:

- Build on previous evaluations of regulatory performance, e.g. Coglianese C. (2012)[17], US Institute of Medicines and Health Canada's LOGIC model

- Update the PRAC framework for impact evaluation

- Develop modelling methodologies (ENCePP SIG to update methodological guidance)

- Consider innovations in technology (social media, WebRADR etc.)

- Establish systematic and shared data collection with industry, regulators and other stakeholders

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[17] Coglianese C. Measuring regulatory performance. Evaluating the impact of regulation and policy. Organisation for Economic Co-operation and Development (OECD). Expert Paper No. 1; August 2012. Available at http://www.oecd.org/gov/regulatory-policy/1_coglianese%20web.pdf

- Complete partnership engagement with stakeholders, representing the bigger picture of whole health care systems

The following **key deliverables** are proposed:

- ENCePP Special Interest Group (SIG) to deliver novel analysis and methodologies

- Relevant GVP and other regulatory guidance to be expanded to cover impact aspects

- Risk communication strategy (SCOPE Joint Action) should continue

- Revision of the PRAC Impact Strategy work plan

Suggestions made during the workshop for taking these recommendations forward are provided below. The Agency in collaboration with PRAC and the EU regulatory network will consider these proposals taking into consideration the potential benefits for public health and the resource implications for the EU regulatory network. It is envisaged for a prioritised implementation plan to be made public in Q2 2017.

Proposed actions	
1. Revision of the framework for impact evaluation	
1.1	Update the framework for EU pharmacovigilance impact research for all involved stakeholders such as regulators, academia, HCPs, patients, healthcare system providers, medical councils, HTA bodies etc.;
1.2	Review the methods of impact evaluations of similar (regulatory) systems (e.g. from published literature, Health Canada's LOGIC model, US Institute of Medicines, environmental epidemiology etc.);
1.3	Consider revision of guidance to address the regulatory and operational challenges of survey studies, PASS and effectiveness studies, including combining exposure data from different sources and countries;
1.4	Define process and outcome indicators for measuring impact of key pharmacovigilance activities;
2. Systematic collection of impact relevant data considering the need for, the nature of and the approach to collection	
2.1	Support transparency measures and platform for sharing impact relevant data, e.g. PASS protocols and results, effectiveness studies among MAHs and the EU regulatory network;
2.2	Access to and use of electronic health data providers, e.g. electronic health records, disease registries etc.;
2.3	Establish a set of publicly available activity indicators (KPIs) for prioritised EU pharmacovigilance activities;
3. Robust methodologies for measuring health impacts of pharmacovigilance activities	
3.1	Explore methods for predictive modelling of drug utilisation data of withdrawn products to measure changes in morbidity or mortality;
3.2	Review examples of interrupted time series (ITS) regression analysis and other time series methods to measure impact of regulatory actions on health outcomes;

Proposed actions	
3.3	Review examples of validation methods for health outcomes identified with routinely collected healthcare data;
3.4	Explore triangulation techniques to quantitatively measure engagement in risk minimisation;
3.5	Explore real time monitoring of drug usage in population-based electronic health records to identify inappropriate patterns of use;
4. Establishing collaboration with novel information technology providers	
4.1	Consider collaboration with big data providers and social media platforms to explore the value of novel data mining and analytical approaches to complement impact research;
5. Active engagement and capacity building with patient communities and healthcare professional bodies to support impact research	
5.1	Launch awareness campaign for patients and HCP to strengthen engagement with the EU regulatory and pharmacovigilance system;
5.2	Establish a process for systematic involvement of patient and HCP organisations/bodies and healthcare providers in evaluation of effectiveness of risk minimisation;
5.3	Establish international format and quality criteria for targeted benefits and risks communications;
6. Development of a process for identifying relevant intended (and unintended) public health outcomes of regulatory decisions	
6.1	Identify relevant public health criteria for key regulatory decisions;