Medicines & Healthcare products Regulatory Agency

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**By email to: claire.cope@acmedsci.ac.uk**

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Thank you for the opportunity to provide input to the Academy's study to explore how evidence that originates from different sources (e.g. randomised clinical trials and observational data) is used to make decisions about the risks and benefits of medicines. Our response is attached and I hope it is helpful for the purposes of planning the project workshops that are due to take place soon.

We are content for our response to be published. However, we would like to see the context in which the response or any extracts from the response are presented before it is published if that would be possible.

We are pleased to have the opportunity to participate in this initiative and if there are any questions about any aspects of our response or if we can provide any other assistance, please do not hesitate to contact us.

Yours sincerely

**Dr Ian Hudson, CEO, MHRA**

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## RESPONSE

**Q1. The overarching aim of the workstream is to better understand how society uses evidence to judge the risks and benefits of medicinal products. In your view, what are the key factors underpinning this process that the Academy should consider? Please highlight any related activities that the Academy should be aware of and should seek to engage with.**

MHRA considers that the following are key factors to consider:

- robustness and extent of the evidence
- the potential public health and/or personal impact
- who carried out the research, conflicts (and perceived conflicts) of interest
- differences in scientific opinion
- where, how and by whom the information is communicated

The planned workshops are an appropriate way to gather information as long as the participants are fully representative of the general population.

See also questions in response to Q7.

**Q2. When evaluating the risks and benefits of medicinal products, what are the *strengths* of evidence that originates from different sources?**
***Please consider a range of different sources of evidence, including case reports, observational or large databases, randomised clinical trials, meta-analyses, evidence from evolving or novel trial designs, and data emerging from citizen science, among others. Please provide examples and case studies to illustrate your arguments where appropriate.***

As part of the licensing process of a medicine, it is necessary to generate data in an unbiased systematic approach. Randomised control trials (RCTs), especially double blind, offer the greatest opportunity for evaluating the beneficial effects and provide the strongest evidence base at a time when knowledge about the medicine is limited, such as before licensing. Forms of RCTs that are not double blind are of value in certain situations.

In some experimental situations, in particular for interventions where benefits are expected to be dramatic, randomisation or replication of evidence in multiple RCTs may not be necessary. Some experimental situations offer the opportunity to use different methods for evidence generation including novel experimental approaches. These may include adaptive clinical trial designs and, for example, basket trials. Each of these methodologies has their place and scientific advice is offered as a forum by regulators, for developers to discuss the suitability of different methods of evidence generation in different scenarios and a pilot in ongoing at EMA discussing possible ‘adaptive pathways’ to discuss the optimal evidence generation, using all available methodologies including use of ‘real-world data’ to meet the demands of the multiple public stakeholders, before and after marketing authorisation.

Meta-analyses, a systematic analysis of similar studies or trials that may or may not be randomised can also be a useful source of evidence in decision making. Conduct of, and inferences from, meta-analysis rely on assumptions around similarity of design and outcomes in contributing studies. The assumptions required for valid inference are even stronger in network meta-analyses that also include indirect ('between-study') comparisons and these need to be clearly presented and interpreted with caution.

Medicines can have adverse effects that are rare or only become apparent after a long latency period or duration of treatment and are therefore not detected in RCTs. Further, patients treated in routine clinical practice, outside of a structured RCT, can have more complex clinical histories so the generalizability of data should be considered. Observational data are vital in exploring safety signals and obtaining a more complete picture of the benefit risk profile of a medicine throughout the post-licensure product lifecycle particularly when further RCTs are unethical or unfeasible.

Individual adverse event case reports or case series can provide extensive detail on potential cases of unrecognised adverse events and are a vital tool in raising new safety signals in both very recently marketed and more established medicines. One of the main strengths of reporting schemes such as the Yellow Card scheme (YCS) are that they are open to reports from anyone be they patients or carers, health care professionals, the media, or marketing authorisation holders.

Epidemiological studies, particularly given advances in study designs and statistical methodologies, allow more robust examination of potential adverse events by placing a signal in context and enabling comparative analyses to explore potential causality or further establishing effectiveness and the absence of safety concerns. Studies or registries with active data collection can provide very detailed data on potential confounders and allow for the validation of data. However, increasingly linked healthcare databases are available and they can rapidly provide detailed data on a large number of patients including comparator cohorts.

**Q3.When evaluating the risks and benefits of medicinal products, what are the *limitations* of evidence that originates from different sources? Please consider a range of different sources of evidence as outlined in question 2. Please provide examples and case studies to illustrate your arguments where appropriate.**

Both RCTs and meta-analyses are limited in terms of duration of observation by nature and therefore provide information about common adverse effects that appear early after exposure. They are often expensive to conduct due to the intensity of follow up notwithstanding the duration. While very useful for demonstrating the effectiveness of the drug, due to their relatively short follow up period most RCTs provide limited data on rare adverse effects or of those adverse events that appear late. Sometimes, infrequent adverse events require larger population of patients that may not be possible in a randomised setting.

While case reports are an important tool for raising signals, they require an individual to suspect a reaction which can lead to bias and varying levels of under-reporting and they cannot be used on their own to infer causality as they need to be placed in a wider context. There are well documented known limitations to epidemiological studies principally the potential for random and systematic biases that lead to wrongly interpreting a crude association as a causal relationship although the same issues can also mask a true relationship. Even with appropriate study design and the use of complex statistical techniques particular care is still required in interpreting epidemiological studies.

The use of large linked patient databases to conduct epidemiological studies presents unique limitations, for example a lack of data on adherence to treatment or validation of diagnoses. The increased availability of databases has also led to opportunities for data mining. However, this can lead to chance findings being wrongly interpreted as true associations.

**Q4. Please provide details of any further examples or case studies that it would be useful for the project to consider. These examples/case studies must relate to medicinal products. We**

**will not consider surgical interventions, medical devices, screening procedures and so on.**

### *a) How MHRA prioritises signals detected through spontaneous data (based on strength and limitations of evidence for causality and potential public health implications) - impact analysis and RPPS*

The MHRA uses two published tools to aid understanding of the potential impact of safety issues, and in their prioritisation. These tools are broadly used to determine the strength of evidence and public health implications of a potential side effect identified through the YCS; the UK's spontaneous reporting scheme for Adverse Drug Reactions (ADR).

Impact Analysis[1] is used on occasions where it is unclear whether regulatory action should be taken based on the evidence available. There are two key components to the scoring system; the first being a strength of evidence assessment which considers statistical disproportionality of the event for the drug of interest, factors such as temporal association, confounding factors and the extent of available information from the spontaneous cases, and as assessment of the biological plausibility of the event. The second component is the likely public health impact if there is a true association. This considers numbers of cases per year, the health consequences of the ADR and the reporting rate. When these factors are considered a score is generated indicating whether action is required, and what course of action is appropriate. These outputs are then considered by a meeting comprising scientific and medical expertise.

The Regulatory Pharmacovigilance Prioritisation System (RPPS)[2] builds on the elements used in Impact Analysis, additionally taking into account public perceptions of the ADR and Agency obligations to help determine a priority for regulatory action. RPPS is calculated for every validated signal arising from spontaneous data. Agency obligations cover ministerial interest in the drug, together with the Agency's role in regulating the drug in the European system. Factors taken into account when considering public perceptions include any significant media attention in relation to the issue, potential 'fright factors', advice from lay advisors or the potential for misperceptions of the safety profile to have an adverse impact on public health. Outputs are reviewed by a multidisciplinary team who will agree the appropriate course of action.

1) Waller P, Heeley E, Moseley J. Impact analysis of signals detected from spontaneous adverse drug reaction reporting data. Drug Safety. 2005; 28 (10):843-50
2) Seabroke S, Waller P. Development of a Novel Regulatory Pharmacovigilance Prioritisation System. http://link.springer.com/article/10.1007/s40264-013-0081-3

### *b) Triggers from a range of data sources that have resulted in a review of the evidence and expert advice*

The following provides a series of examples of safety signals that have been reviewed by the Agency and were triggered by a variety of different sources.

#### 1. Alteplase – review of benefit:risk balance in ischaemic stroke

A retired stroke physician contacted MHRA with a number of concerns over the pivotal RCT data underpinning the licence. An initial evaluation by MHRA of these concerns, together with any data that had become available since the benefit:risk of alteplase in stroke had been last reviewed was considered by the Commission on Human Medicines (CHM) who advised that the data had no impact on the current licence. An article in the lay press was published with the headline 'Thousands of deaths blamed on stroke drug'. To prevent any further loss of confidence by the public and medical community in this medicine (which is the only authorised treatment for acute ischaemic stroke) an ad hoc Expert Working Group (EWG) of the CHM was established to review all sources of evidence, including those of the physician, on the efficacy and safety of alteplase when used to treat stroke in UK clinical practice.

## 2. NSAIDS and cardiovascular risk

The withdrawal of the selective COX-2 inhibitor rofecoxib due to cardiovascular side-effects (heart attack and stroke) identified in the VIGOR[1] and APPROVe[2] trials led to numerous reviews of the other non-steroidal anti-inflammatory drugs. The evidence used in these assessments included data from clinical trials conducted by the marketing authorisation holders (including MEDAL[3], CLASS[4], TARGET[5], APT[6], PReSAP[7]), published meta-analyses of clinical trial data (including one of patient-level data[8]), meta-analyses of existing epidemiological studies and 4 newly commissioned case-control studies funded by the European Commission as part of the Safety Of non-Steroidal anti-inflammatory drugs (SOS) Project[9], and published pharmacoepidemiology studies (including meta-analyses and systematic reviews). Overall these data show that coxibs and traditional NSAIDs as a class are associated with a small increased risk of heart attack and stroke; that the risk appears to be greatest for coxibs and the traditional NSAIDs diclofenac and high-dose ibuprofen, and lowest for naproxen and low-dose ibuprofen. These assessments led to the introduction of warnings on cardiovascular risk for all coxibs and NSAIDs. The strongest warnings were introduced for coxibs, diclofenac and high-dose ibuprofen, reflecting the apparent greater risk.

For the newer coxibs, the available randomised placebo-controlled trial data were sufficient to warrant contraindications and stronger warnings regarding cardiovascular risk in 2005. However, for the older traditional NSAIDs diclofenac and ibuprofen, placebo-controlled trial data were limited. Whilst initial data from coxib vs tNSAID trials suggested that diclofenac and high-dose ibuprofen had a similar risk to coxibs[3,4], the balance of evidence to warrant stronger additional warnings in-line with the coxibs was reached more recently following the accumulation of published pharmacoepidemiological data and a new analysis of the initial trial data[8].


1 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000 Nov 23;343(21):1520-8.

2 Bresalier RS, Sandler RS, Quan H, et al, for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial. Cardiovascular events associated with rofecoxib in a colorectal adenoma prevention trial. N Engl J Med 2005; **352:** 1092–102.

3 Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L; MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet. 2006 Nov 18; 368(9549):1771-81.

4 Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000 Sep 13;284(10):1247-55.

5 Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, Gitton X, Krammer G, Mellein B, Gimona A, Matchaba P, Hawkey CJ, Chesebro JH. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet. 2004 Aug 21-27;364(9435):675-84.

6 Bertagnolli MM, Eagle CJ, Zauber AG, et al, for the APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006; **355:** 873–84.

7 Arber N, Eagle CJ, Spicak J, et al, for the PreSAP Trial Investigators. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006; **355:** 885–95.

8 Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet published online May 20, 2013: http@//dx.doi.org/10.1016/S0140-6736(13)60900-9

9 Safety of non-steroidal anti-inflammatory drugs (SOS) Project: http://cordis.europa.eu/project/rcn/89349_en.html


## 3. Pioglitazone and bladder cancer

A study conducted by the marketing authorisation applicant (MAA) prior to authorisation showed bladder changes suggestive of early cancer in male rats. However, the finding was not seen in other

species, and its relevance to humans was unclear. Clinical trial data did not show any evidence of a similar signal in humans prior to authorisation. As a result the safety of pioglitazone was closely monitored with the MAA being required to carry out an additional 2-year mechanistic study in rats and an observational study conducted using the Kaiser Permanente Northern California (KPNC) database. The issue was reviewed repeatedly between 2005 and 2010 but a risk in humans was not confirmed although the ongoing KPNC study suggested a slight trend to an increased risk of bladder cancer with greater duration of exposure (>24 months) and with greater cumulative dose. Following an increase in spontaneous reports of bladder cancer from healthcare professionals in France and updated results from available studies (which were consistent with a very small risk in humans), another European-wide review was initiated. The conclusion was that data from all sources does not strongly support an association. Nevertheless, a consistent, albeit not always statistically significant trend to increased risk has been reported from a number of sources, particularly in association with longer term use. Studies are ongoing to further characterise the risk via observational studies and product information has been updated.

**4. Sodium valproate – risk of developmental disorders in children born to mothers taking the drug during pregnancy and the benefit/ risk of valproate in women of childbearing potential**

The triggers for this Europe-wide review included publication of new studies and public and political concern about risk awareness among patients prescribed valproate for epilepsy and bipolar disorder.

The results of studies published in 2013 improved our understanding and allowed us to better characterise the risk of the longer term neurodevelopmental effects following in utero exposure to sodium valproate. The studies have highlighted that in some children the effects appear to persist and manifest as a range of neurodevelopmental abnormalities and autism spectrum disorder. These emerging data suggested that the risk of neurodevelopmental delay and autism spectrum disorder may be independent of maternal confounders [1-4].

The studies clarified the magnitude and nature of the risk and the review resulted in appropriate risk minimisation measures being introduced to help optimise safe use of sodium valproate in girls and women of child bearing potential and reduce the risk of unintended pregnancy exposures.

1. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kenner A, Lip race JD, Pennell PB, Privateer M, and Luring DW. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD Study): a prospective observational study. Lancet Neurology. 2013, March;12(3): 244-252.
2. Bromley R et al. The prevalence of neurodevelopment disorders in children prenatally exposed to antiepileptic drugs. J Neural Neurosurgery Psychiatry 2013; 0: 1-7
3. Christensen J et al. Association of sodium valproate with Risk of Autism Spectrum Disorders and Childhood Autism. JAMA, April 24, 2013. Vol 309, No 16.
4. Veiby, Gyri et al. Exposure to antiepileptic drugs in utero and child development: A prospective population-based study. Epilepsia. 2013. Aug; 54(8): 1462-72

**5. Natalizumab and risk of PML**

In light of promising efficacy data and a small number of PML case reports, Natalizumab was authorised in Europe in 2006 given a positive short-term benefit risk profile but with an extensive Risk Management Plan (RMP) aimed at further characterising the PML risk and minimising it optimally.

The RMP included requirements for a range of clinical (randomised / open-label) safety & efficacy, non-clinical (immunology, genetics), registry-based, cross-sectional and longitudinal cohort studies as well as comprehensive and regular review of cumulative spontaneous reporting data. Regular consideration of relevant findings from non-MAH sponsored clinical, non-clinical, ex vivo and observational studies was also required.

Evidence from hundreds of PML cases reported globally from all the above sources was critically appraised and where appropriate, used to inform the development of extensive risk minimisation measures including a Patient Alert Card describing the risks, key symptoms and time course of PML

and an extensive Physician's PML Information and Management Guideline including all of the above information plus detailed PML diagnostic criteria and treatment options.

On occasion, after a medicine has been licenced, safety data arising from RCTs conducted to advance the applicability of the medicines for other uses contribute to safety information. Such information while not frequent, provide valuable insight into the safety aspects and risks associated with special groups and influences the subsequent use of the medicine.

***c) Some examples of improving communication in the patient information leaflet including the involvement of the CHM EAGPPE in various communications on safety issues directly to patients.***

When providing information for patients through the statutory patient information leaflet (PIL) the MHRA refers to both international and national guidance in the area of content development and information design to ensure that the information provided is accessible to the reader. In particular the UK has published "Always Read the Leaflet – getting the best information with every medicine" which has been widely taken up by those who develop the statutory PIL. It includes detailed guidance on how to test the information with patients and the public to ensure that those who are likely to rely on the PIL will be able to find and understand the key messages for safe and effective use. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/391090/Always_Read_the_Leaflet___getting_the_best_information_with_every_medicine.pdf

We involve our expert advisors including patients and the public through the Patient and Public Expert Advisory Group of the Commission on Human Medicines CHMEAGPPE to advise on the suitability of both the content and the layout of the information specifically for patients and the public. The CHMEAGPPE has also advised on the way in which publicly available articles on drug safety issue should be prepared when the issue is sufficiently important to warrant an article for patients in addition to informing healthcare professionals of new safety information. Examples of such patient articles include one for domperidone [https://assets.digital.cabinet-office.gov.uk/media/54730802e5274a130300002d/con418525.pdf] and one for simvastatin

http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con199557.pdf.

The CHMEAGPPE has advised on the provision of common sets of information for those medicines which are commonly prescribed and in addition can result in high levels of adverse drug reaction reports. Such examples include the statutory PILs for warfarin, isotretinoin and paracetamol.

**Q6. Please highlight any broadly applicable principles that should govern the presentation, interpretation and weighting of evidence about medicinal products. We are focussing on principles that support patients, the public, healthcare professionals and the media to better consider the risks and benefits of medicinal products.**

***Basic principles adopted by the MHRA:***

***a) when presenting evidence***

- A brief article that refers readers to other references is likely to have greater impact than a lengthy one
- If appropriate, use tables to present data clearly, and use bullet points to emphasise key points
- Keep language as clear as possible and use short sentences.
- When describing risk, try to use absolute values. State how many cases there have been and the frequency of the concern - absolute risk as well as, or instead of, relative risks - to put the safety issue into a public health context.

- Try to avoid subjective statements which could be open to differing interpretation. For example, the sentence: “drug A has a low risk of cardiovascular effects” will only be consistently interpreted if it is accompanied by a qualifier stating what is meant by “low” (e.g. < 1/1000 patient years). Also provide with information on the type of cardiovascular effect (ie, serious or non-serious, cardiac, thrombotic, peripheral vascular etc).
- Avoid hanging comparators, eg “drug A is associated with an increased risk of cardiovascular effects”. Increased compared to what? Better to say: “People who take drug A are more likely to have serious cardiovascular side effects (eg, X, Y, Z) than people who do not take drug A.”
- Take care when making comparisons with other drugs. Comparators and (when appropriate) doses/dose-ranges should be clearly stated: eg, “diclofenac is associated with cardiovascular risks that are higher than the other non-selective NSAIDs, and similar to the selective COX-2 inhibitors. Naproxen and low-dose ibuprofen are still considered to have the most favourable cardiovascular safety profiles of all non-selective NSAIDs.”

***b) when interpreting and weighting evidence from a range of sources***

Both RCTs and epidemiological studies should be rigorously conducted following published guidelines to ensure robustness. In particular, there is an obvious need for the primary presentation of data by study authors to be clear and comprehensive in order to allow a thorough assessment of the study by all stakeholders. Again, published guidelines such as those from CONSORT or STROBE should be followed.

Careful interpretation of RCTS and observational data is always required. The Bradford Hill criteria provide us with a framework for assessing causality but should be primarily used as a guide as assessment may be limited by current wider scientific knowledge. In principle, in the hierarchy of evidence, meta-analyses of RCTs provide the strongest evidence. However, all available evidence, regardless of source, should be considered and limitations of RCTs may mean that true findings are only seen in observational data. When weighing up data that is not fully conclusive consideration should also be made to the public health impact and the potential for obtaining further data.

***c) relating to advertising of medicines***

Only medicines that have met the standards required to have been granted a marketing authorisation or registration (herbal or homeopathic medicines) may be advertised.

All advertising for medicines must:

a. comply with the particulars listed in the Summary of Product Characteristics;
b. promote the rational use of the product by presenting it objectively and without exaggerating its properties;
c. not mislead.

Additional restrictions apply to advertising to the public including bans on advertising to children, comparisons between named products, guarantees, and recommendations by healthcare professionals or celebrities.

Prescription only medicines may not be advertised to the public. This does not prevent the provision of balanced and factual information about treatment options available.

**Q7.Concerns have been raised about how industry funding impacts on the validity, or the perception of validity, of evidence. For example, the ability of academic researchers funded by industry to remain impartial when evaluating evidence has come into question. How should conflicts of interest be addressed? How important is industry funding in generating and analysing evidence? Other than industry sponsorship, what are other potential sources of conflicts of interest?**

**The importance to public health of industry funded evidence and how/whether the funding source influences interpretation of post-marketing data**

Marketing authorisation holders have an obligation to ensure a positive benefit risk profile of their products pre- and post-licensing. Data generated by industry or in industry-sponsored studies is very important in providing strong evidence of efficacy and safety to support a licencing application, evidence of effectiveness and safety in routine clinical practice, assessing specific safety signals, and monitoring the impact of risk minimisation measures. One role of the regulator is to ensure that this data is robust by ensuring that study protocols are clear and results fully presented, particularly by ensuring industry is following regulatory guidance and requirements. Industry also has a role in interpreting data on their products and planning actions based upon it. However, independent regulatory assessment will always take precedence over this and further independent advice on the interpretation is sought to inform this assessment. Data from all sources is considered by the MHRA and in consultation with the advisory groups such as Commission of Human Medicines and its subsidiary expert advisory groups.

External advisory committees such as the CHM and its expert advisory groups (EAGs) are subject to a code of practice on interests in the pharmaceutical industry. Members of CHM are not permitted to hold any personal interests (direct remuneration) in the pharmaceutical industry as a condition of their appointment. All members are required to return a declaration of interests each year and these are published in the Human Medicines Regulations Advisory Bodies Annual Report.

https: www.gov.uk/government/uploads/systemuploads/attachmentdata/file/446872/Human Medicines Regulations 2012 Advisory Bodies Annual Report2014.pdf (code of practice p.127)

Interests taken into account include personal interests (e.g. shares, lecture fees, consultancy), non personal interests (e.g. departmental support) and "any other" interests" of relevance. "Other interests" may include, for example, an individual having made public statements about a particular product or having been involved with a charity or pressure group that has an interest in the outcome of advice being given. All conflicts of interest are carefully considered and reviewed on a case by case basis in accordance with the code of practice. Conflicts perceived to substantially affect a member's impartiality may result in restrictions to participation or exclusion from the discussion.

**Q8. Please outline any past, current or planned initiatives to examine how patients, citizens and healthcare professionals (and those who seek to inform them) evaluate scientific evidence about medicinal products.**
***Please specify any questions you feel it would be useful for the Academy to explore in our formal dialogue work with patients, citizens and healthcare professionals, and any evidence from previous public dialogue.***

**a) References to work we have done or are planning to examine how patients/HCPs evaluate evidence**

The MHRA and its Committee on Safety of Medicines (now the Commission on Human Medicines) has undertaken extensive work on how to present medicines safety information to patients (see the report "Always Read the Leaflet: Getting the best information with every medicine"). This includes guidance on 'user testing' of medicines safety information for patients (see pages 26, 89 and 97 of the above report).

**b) Suggestions for questions that should be explored at the workshops are:**

i. What is more important to a) patients b) HCPs: who generated the evidence; what type of evidence it is (RCT, observational study, case report, citizen science etc.); how and from whom they heard about it (media, healthcare professional, friend, relative, regulator, social media, internet/web sources, scientific journal etc.)? What is their reasoning? Do they seek further information and if so who/where from?

ii. Once an organisation's reputation has been tarnished, for whatever reason (true or false), can it ever regain trust?
iii. What would make you (dis)trust information /evidence/an organisation?

**Q9. What are the most effective ways of communicating evidence to various stakeholders and engaging with them about such evidence?**
***Please consider a wide range of stakeholders, including patients, the public, healthcare professionals (general practitioners, nurses, pharmacists, clinicians, etc.), and the media, among others*.**

**Work we have done on the effectiveness of communicating evidence to health professionals in terms of presentation, content and mechanism**
When the MHRA takes regulatory action to address safety issues with marketed medicines, this action will involve presenting evidence to health professionals to inform their prescribing practices. The MHRA has monitored and evaluated the effects of its regulatory action on health professionals' prescribing practices by conducting four case studies (A Thomson *et al*., 'Monitoring and Evaluating the Effect of Regulatory Action: Some Recent Case Studies' *Therapeutic Innovation & Regulatory Science*, July 2015; vol. 49, 4: pp. 473-482., first published on February 23, 2015).


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