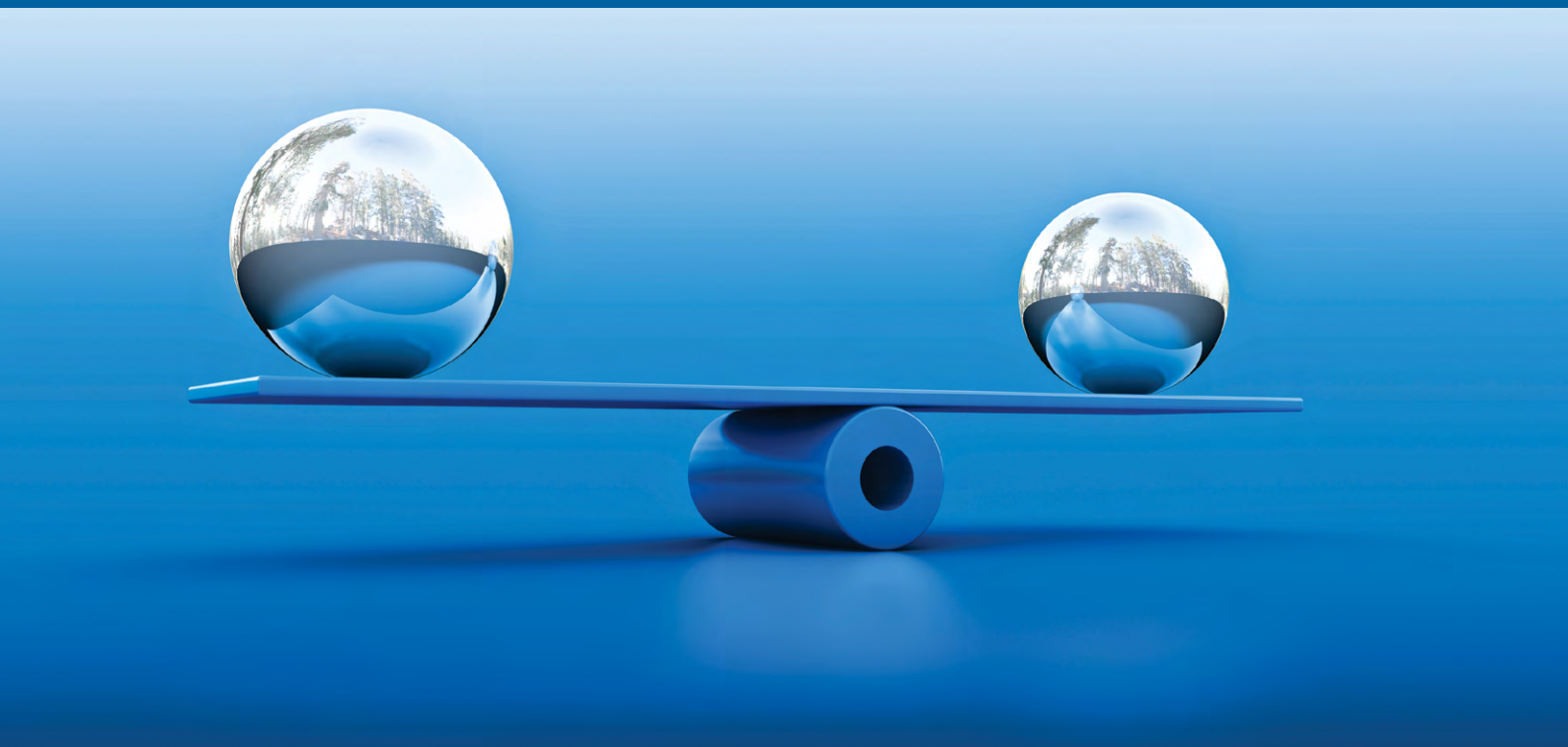
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Best expertise vs conflicts of interests: Striking the right balance

Workshop report

Report from the public workshop hosted by the European Medicines Agency in London on 6 September 2013



European Medicines Agency engages with stakeholders on its policy on conflicts of interests for experts

Guido Rasi opens the debate

Every industry across the world is challenged by conflicts of interests. However, in the healthcare arena, where conflicts of interests are often regarded negatively, the issue is particularly complex.

The European Medicines Agency (EMA) takes conflicts of interests of its experts very seriously. Over the past few years, the Agency has taken comprehensive steps to strengthen its handling of such conflicts, and believes that this approach must continue.

However, regulatory bodies are faced with a shortage of available expertise, because most conflicts of interests exclude the expert from taking an active role in decision-making processes. The EMA currently has some 5,400 experts on its database, yet many of these are restricted with respect to their level of involvement in Agency activities because of their declared conflicts of interests related to their involvement in the pharmaceutical industry.

Recognising this problem, in September 2013 the EMA hosted a workshop to look at how it can achieve the right balance between ensuring the impartiality and independence of experts and securing the best-possible scientific expertise when delivering assessments, without lowering the bar on its conflicts-of-interests policy.

"Highest-quality scientific assessment requires the best scientific experts and protection of the assessment process from undue financial or other interests," said Guido Rasi, the Agency's Executive Director. "We need a robust system to get the balance right between managing conflicts of interests and access to the best expertise to deliver high-quality scientific assessments. This must be underlined by utmost transparency, to allow public scrutiny."

The EMA began to address the issue of conflicts of interests as early as 1994, when its Management Board adopted initial guidance for experts, setting out responsibilities with regard to declaring direct and indirect interests. Since then, the Agency's policy on conflicts of interests for scientific-committee members and experts has undergone a number of revisions, with updates coming more frequently since 2011 (see the 'Historical overview' on p.10).

Guido Rasi said that the challenge is now to define a methodology for identifying the best expertise within the European Union.

"The EMA needs to find a scientific review process that will result in increased trust levels among healthcare professionals and the public. However, we cannot lower the bar for the conflicts-of-interests policy. So, what do we need to do, or to change, to make involvement with the EMA more attractive to experts? Any suggestions made today will be put to the Management Board for consideration when it meets in December. Those that are feasible will be included in the next update of the policy."

Guido Rasi, Executive Director of the European Medicines Agency

A view from the top

To give views from the European institutions on conflicts of interests, Matthias Groote, Chair of the European Parliament's Committee on the Environment, Public Health and Food Safety, was joined by the Chief Scientific Adviser to the President of the European Commission, Anne Glover.

Matthias Groote, Chair of the European Parliament Committee on the Environment, Public Health and Food Safety

Groote began by confessing that it was often the case that conflicts of interests only appeared on the Parliament's agenda once a particular conflict had become apparent. However, he said it was clearly an important issue to the Parliament when creating legislation. "We obviously want the best experts in Europe working on our legislation. Yet, sometimes we don't really appreciate that there is a finite resource of experts. We need transparent and clear rules, and we need to debate conflicts of interests in the public arena. Nevertheless, we also need to bear in mind that we have a limited budget when it comes to assessing conflicts. There is a cost involved, and we need to recognise that."

While admitting that he was attending the workshop primarily to listen and learn, Groote did speculate that agencies looking to work with the best experts may have to consider the need to pay for that expertise in some manner, and recognise current limitations. "If we want the best experts, we have to recognise that they will be involved in science and industry. We need to ensure transparency while looking for a suitable solution," he concluded.

Anne Glover agreed that conflicts of interests is an important issue to get right. "I am absolutely married to the idea that this workshop should try to deliver the best possible way of achieving the right balance when we are seeking out evidence. Sometimes, the drive to try and take everything into account and to produce something that is perfect results in delay after delay. Glover believes that this rarely benefits anyone — particularly not agencies that need to make decisions.

She also believes that trust, in both professional and personal life, is important to everyone, and that most people see it as a prerequisite for effective operation. She said she was surprised when she began working at the Commission to find she was presumed to be guilty until she could prove she was innocent.

"At first I thought it was a bit of a joke, but when you feel you are constantly trying to prove you are trustworthy, it has a big impact on you. I think we need to consider this today. I have worked with industry — I even set up a company. Are we saying that because of this involvement with industry I am fundamentally untrustworthy, that I am suspicious? Surely if we reject someone with broad interests because of those broad interests, we will lose out."

She told delegates that it was time to do things differently, rather than be passive participants in change. In a thought-provoking conclusion, she highlighted Wikipedia, pointing out that it rejected Encyclopaedia Britannica's peer-review model of relying on experts, in favour of allowing readers to post and moderate/validate its content. "There may not be a conflicts-of-interests policy or statement [on the Wikipedia website], but there are still checks and balances — a solid mechanism for checking the validity of information. Wikipedia was a response to the modern world, where our attitude in terms of relying only on experts is not what it used to be."

Anne Glover, Chief Scientific Adviser to the President of the European Commission

Fernand Sauer moderates discussion on the panel

The panel

Moderator
Fernand Sauer, former Executive Director of the European Medicines Agency (EMA).

Academia
Wolf-Dieter Ludwig, Chair, Drug Commission of the German Medical Association.

Rory Breathnach, Head of Small Animal Medicine, University College Dublin, School of Small Animal Medicine.

EMA scientific committees
Daniel Brasseur, Chair, Paediatric Committee (PDCO).

Anja Holm, Chair, Committee for Medicinal Products for Veterinary Use (CVMP).

Scientific advisory groups (SAGs)
Serge Bakchine, Chair, Scientific Advisory Group on Neurology.

Patient groups
Nikos Dedes, President, Positive Voice (Greek association of people living with HIV).

Pharmaceutical industry
Richard Bergström, Director-General, European Federation of Pharmaceutical Industries and Associations (EFPIA).

Non-governmental organisations
Martin Pigeon, Researcher, Corporate Europe Observatory.

Drug bulletins
Pierre Chirac, Editor, revue Prescrire; President, Association Mieux Prescrire.

The heart of the debate

Fernand Sauer, former Executive Director of the EMA, told delegates the aim of the workshop was to answer a simple question in the context of the Agency's regulatory framework:

"To be able to continue to deliver high-quality assessments, how can the EMA balance its need to access the best experts with its requirement to ensure the impartiality and independence of those experts?"

Sauer asked the delegates how the Agency could make it more attractive for experts to get involved, whether the current safeguards in terms of direct and indirect interests were adequate, and what other issues or elements needed to be considered.

Leading the debate was a carefully chosen panel representing academia, industry, EMA committees and scientific advisory groups, patient organisations, NGOs and drug bulletins. As the moderator, Sauer asked each of them to give a brief position statement before launching into a discussion on how best to answer his questions.

Fernand Sauer, former Executive Director of the EMA (moderator)

Several of the panellists called for clarity when it comes to applying the rules. Keeping track of which experts can be involved in which projects, who can vote and who has to leave the room can be very complex, they said.

Representing the drug bulletins, Pierre Chirac believes there is no room for conflicts of interests at the EMA, and that the only way to ensure true independence and impartiality is to impose a complete ban on any conflicting interests. "We are not talking about dirty hands and bad people: we are talking about unconscious influence and subtle psychological behaviours," he said.

Throughout the day, however, three key points kept being raised by panellists and delegates alike as reasons for there being a scarcity of experts: the terminology used to describe both experts and conflicts, the timeframes involved, and the lack of recognition given to experts.

Terminology and classification

The language and terms used to define and explain the various elements of the Agency's conflicts-of-interests policy were identified as being of concern. Panellists suggested that the use of terms such as 'risk' could be deterring many experts. Alongside this was the concern that the lack of clarity surrounding the meaning and consequences of interests and risk levels was equally as off-putting.

Academia representative Rory Breathnach is concerned that the current terms make academics feel they are tainted in some way. "They certainly don't understand risk levels. Tell them they are a risk level 3 and they will feel like they will be thrown out of the building.

"We need to be realistic. Industry will seek out experts and they will fund programmes at universities. It is the policy of most major governments to drive collaboration between industry and academia. Yet there is an implication that academia will be less than honest to get money. I don't know anyone who would state an opinion they don't believe in simply because industry came calling. Academia is there to give information and opinion, which has to stand up to scrutiny. Academics want to be involved, so changing the mind-set about this group will see the panel of experts expand. Everyone will win."

Anja Holm, Chair of the Committee for Medicinal Products for Veterinary Use, agrees that taking the stance that experts need to prove themselves trustworthy is not conducive to persuading them to get involved. "I am sure many experts might feel that, as the leading expert in their field, they don't need to show they are trustworthy. The current wording of the policy actually insinuates risk, or risk to robust decision-making. Most people would find that an insult and it needs to change."

Patients' representative Nikos Dedes is often approached by pharma as an expert, and he knows too well about the scarcity of patient experts. "I feel like the term 'risk' is a presumption of guilt, and I think it leads to a defensive attitude," he said.

"I also think there is a problem with the direct versus indirect classification system. It is ludicrous to give one honorarium of 800 euro for a speech more weight and importance than a million-euro donation to a university by a pharma company."

Academic Wolf-Dieter Ludwig doesn't like the phrase 'possible' or 'potential' conflict of interests. "They are simply a set of circumstances that exist. The question should be whether they have any impact on our professional judgement," he said.

"I also have a problem with the idea of a 'good expert'. What does good expert mean? Does it have to be the most prominent or visible expert, or simply the most competent? In addition, I think we need wider definitions when it comes to direct and indirect interests, and further clarification on which expert relationships are deemed appropriate."

Timeframes

Currently, if an expert has declared certain direct or indirect interests that fall within a five-year period, they will automatically be assigned either risk level 2 or risk level 3. The timeframes for the declared direct or indirect interest are 'current', 'within the past two years' or 'within the past two to five years'. Interests must be declared up to five years after the interest ceases to exist. After that period, it is down to the expert to declare any older, pre-existing conflicts.

Rory Breathnach believes that the two-to-five-year timeframe currently imposed is completely arbitrary. "It seems like it is a figure that was just picked out of the air. How can I be a problem one year, 11 months and 29 days after a declared interest ceases, but fine just hours later? I don't think set

Anja Holm, Chair of the Committee for Medicinal Products for Veterinary Use (CVMP)

Rory Breathnach, Richard Bergström and Martin Pigeon

periods of time should be used. It should be assessed on a case-by-case basis. In fact, experts should be asked if they have a conflict either in terms of the product or a point on the agenda. If they do, they should be automatically excluded."

He suggested that the decision pathway itself should be more transparent. "I will attend meetings where I am told I am a risk level 3, but that following an analysis, I will be allowed full participation. Yet I don't know why!"

Richard Bergström, Director-General, EFPIA

Industry representative Richard Bergström agrees that the timelines should be flexible, especially when it comes to drug development, where the timelines involved are protracted. "An expert could have been involved in the development of a product eight years previously, which is only just coming to market. They will clearly have an emotional attachment to the product, and so should excuse themselves even though they are not required to do so. In general, however, I think that going back five years is too far."

Richard went on to point out that the U.S. Food and Drug Administration strengthened its requirements in terms of timelines but had such problems finding experts that it had to reverse the decision. Its timelines are under five years, but it supports this by more active monitoring, and by extending timelines, where appropriate.

Wolf-Dieter Ludwig was able to share the experience of the German Medical Association's Drug Commission. "We set out our own conflicts-of-interests policy in 2003. We now require a declaration of interests before membership or participation that reaches back three years. This includes both paid and unpaid activities. I do think that the severity of the interest should be linked to its scope or timeframe."

Other members of the panel agreed that the timelines set out under the Agency's policy on conflicts of interests did not meet the needs of the policy's objectives, let alone the drive to increase the number of experts on the EMA database. While Martin Pigeon, representing NGOs, suggested that the timeframe should be specific, Anja Holm suggested that two years should be fine unless the situation involves a product, inwhich case the exclusion should be forever.

Recognition and recompense

When looking at another reason for experts being unwilling to take part, Anja Holm suggested that it was perhaps time for the EMA to turn the issue on its head and to ask, what is in it for the experts? Why should they take part? Currently, they get no recompense and little recognition or gratitude. "They are already working flat out in their own job, so why would they want to work out of hours or at the weekend?"

Serge Bakchine, Chair of the EMA Scientific Advisory Group on Neurology

SAG representative Serge Bakchine agreed that the role of experts is underestimated. "As a clinician, I think it is important to acknowledge that being an expert is a real job. Reading reports of thousands of pages at short notice, travelling, etc. It can be hard for experts to decide whether or not to get involved for these reasons alone," he said.

With the promise of little or no compensation and scant recognition, experts have to weigh up the consequence of renouncing any work with industry, such as not attending industry-sponsored conferences." [NB. Under the current EMA policy, attending a conference is not prohibited. However, receiving an honorarium from a pharmaceutical company for attending a conference is not allowed.]

Martin Pigeon added: "Agencies are not attractive to scientists because they know that it doesn't pay and it is hard to get recognition for their work. They are involved in work that won't be published. It is little wonder that it is not seen as a great career option for younger people."

As a scientific-committee chair, Daniel Brasseur agrees that experts are doing a marvellous job that no one knows about. However, he also believes that it is not about the recognition and recompense, but more about the time involved. "If an expert works on a specific project, who gets compensated for their time? It is also interesting to note that you will often see a CV that mentions work done on writing a report, but how often will you see work done as an expert for the EMA mentioned?"

This point was echoed by other panellists, who pointed out that when clinicians or academics take part in projects they have to arrange locum cover.

Self-regulation — will it work?

When it comes to ensuring that experts abide by the rules and fully disclose all interests, the panel agreed that failure to do so should have significant consequences that are far reaching, including a complete ban from serving as an expert.

However, most of the panellists felt that self-regulation was possible. As well as the checks done by the EMA, the expert world is quite small, and so a sort of peer-review system will be in place. If someone has not declared an interest, many of their peers will be aware of this and will take steps to rectify the situation, the panel said. In some cases, this may take the form of whistle-blowing, or more simply naming and shaming. However, in most cases, the very knowledge that they will be under scrutiny should deter those experts who do not want to declare all their interests.

The panel also agreed that, when it comes to decision-making, the structure of the scientific committees to some degree also acts as a safeguard. No one expert is the overall decision-maker, so no one expert can drive the full decision.

Intellectual or financial interests

One topic that engendered much debate was the need to differentiate between intellectual and financial interests. It was agreed that it is harder to quantify or measure the impact of any intellectual interest than it is a financial one. Where a financial interest will leave a trail, as in the case of ownership of shares or payments for services, an intellectual interest may well be hidden. A degree of speculation may therefore be required.

The panel also suggested that unintended bias as a result of that intellectual interest may be equally as impactful as intended bias. For example, a former employee who had a poor experience at a company may, in fact, unconsciously let this intellectual interest cloud their evidence.

Nikos Dedes, Founder and Chair, Positive Voice

Pierre Chirac, journalist

Martin Pigeon, Corporate Europe Observatory

The pharma conundrum

The very nature of the relationship between regulators and the industry means that experts often find themselves caught between the two sides.

"The biggest assets of the industry are the people and brains working in it. Nevertheless, we increasingly rely on the brains outside. We seek out the best experts. Even if we don't hire them, we want to work with them. So I am not surprised we are running out of experts," said Richard Bergström.

"Medicines are not developed just in the lab, but also in the clinic. Pharma wants to work in partnership. We are spending more on external R&D with academia and other partners. For example, Europe has the largest public-private initiative: the Innovative Medicines Initiative.

"Perhaps we also need to separate personal and institutional relationships. Yes, discount experts who sit on company boards, because they will be biased, but should we disqualify a professor of the Karolinska Institute because the institute gets money from industry?" he asked.

"There is a public perception that if you work for industry, you are somehow dirty," agreed Martin Pigeon. "But the policy is not about chasing morally dubious people, it is about protecting public administrations.

"The fact that it is more difficult to find independent experts is a consequence of a long-term industry influence strategy to prevent those experts from being used against their employers," he added.

Pierre Chirac is concerned about the assumption that experts involved with the pharmaceutical industry offer the best expertise. "In reality, there is overwhelming evidence that any conflict of interests is a threat to patient health."

"Work at agencies should be based on evaluation of raw data from clinical trials carried out by competent and independent people or experts. There are plenty of experts willing to contribute who are well informed and independent. Scientists cannot be independent from the sponsor if they are under pressure to publish or perish, a point raised by many studies appearing in journals such as Nature. The EMA should therefore rely on internal staff and experts with no links to industry."

How can these problems be overcome?

Having identified a host of reasons that might be deterring and preventing experts from taking part in EMA activities, the panellists were asked what possible solutions there might be to overcome these challenges. The panel was adamant that the first step must be for the EMA to address its terminology in terms of risk and conflicts, and to reassess the validity of its timelines. As well as these suggestions, the panellists outlined a number of changes that might improve access to expertise.

Flexibility

Many of the panel suggested that perhaps applying stringent rules across the board with no room for manoeuvre is, in itself, closing the door to experts. They all agreed that it was right and proper for the decision-making board to be conflict-free. However, several panellists suggested that for SAGs and other ad hoc groups, there should be flexibility. This is even more important when it comes to specialist subjects and areas such as veterinary medicine or orphan products. In some areas, setting the bar too high is probably choking expertise, they concluded.

Several of the group suggested that, in certain situations, the EMA should allow other groups such as scientific societies to nominate experts, thus widening the pool of available experts.

Sponsorship

Given the need for experts to attend conferences and congresses to maintain and expand their knowledge, and given that many events are sponsored by the industry, it is hard for an expert to service their knowledge and still be available for EMA activities. Serge Bakchine suggested that national agencies or even the EMA should look at sponsoring experts to attend these events. Not only would this avoid the link with industry, but it would mean the EMA had access to well-informed experts."

Wolf-Dieter Ludwig, Member of the EMA Management Board

More expert witnesses

Experts who have been assigned a risk level of 3 are probably experts working at the coal face, albeit probably for industry. However, they may well possess the greatest level of expertise in their area.

Richard Bergström agrees that the concept of expert witnesses could be used more. "That way we could bring in the people who have worked on a product from the beginning. Yes, they will be biased, it's his/her baby, but the fathers and mothers of products deserve to be listened to. They will add knowledge to the process. Then they simply leave and a decision can be made."

"Scientists with conflicting interests whose contribution is seen as indispensible for scarcity reasons should be called as expert witnesses. After all, they have no decision-making powers," agreed Martin Pigeon.

Daniel Brasseur, Chair of the EMA Paediatric Committee

Rory Breathnach, Head of Small Animal Medicine, University College Dublin

View from the European Commission, EU agencies and NCAs

The EMA invited representatives from a number of EU bodies and national competent authorities (NCAs) to share their experiences and thoughts when it comes to dealing with conflicts of interests. Among those present were:

- Bob Van Hoorde, European Commission;
- Manuel Szapiro, Secretariat General, European Commission;
- Aginus Kalis, Dutch Medicines Evaluation Board and EMA Management Board member;
- Pat O'Mahony, Irish Medicines Board and EMA Management Board member;
- Rannveig Gunnarsdóttir, Icelandic Medicines Board;
- Johan Giesecke and Rebecca Trott, European Centre for Disease Prevention and Control (ECDC);
- Dirk Detken, European Food Safety Authority (EFSA).

All the representatives agreed that, while huge strides have been made in their own agencies, there was still room for improvement. All agreed that they also face challenges when it comes to the number of experts available to them, and many have their own hurdles to overcome.

In Iceland, for example, the Icelandic Medicines Board is faced with a small community, so many experts have had conflicts in the past. However, it is actually a legal requirement for experts to sign a declaration stating that they have no interests.

Prohibiting the use of experts in EMA activities who have, or have had, any involvement with industry, as well as having more scientific assessments carried out by employees of NCAs, were also raised as possible approaches to better track conflicts of interests.

The ECDC revealed that they have more of a problem when it comes to personal interests than financial ones, while the EFSA representative told delegates that it was taking a careful look at the wider decision-making process, rather than focusing on one expert. "We are trying to identify where there is room for improvement, while taking steps to differentiate between a breach of trust and a breach of the rules."

Finally, the Commission representative was clear that it would not tell agencies what to do. He did, however, remind delegates that it had published guidelines that can be used to draw up prevention and management policies.

Björn Lemmer, European Parliament representative of the EMA Management Board (left) and Sir Kent Woods, Chair of the EMA Management Board

Closing remarks from the European Medicines Agency

Noël Wathion, European Medicines Agency

Noël Wathion, Head of Patient Health Protection

"We have listened to our stakeholders today and will consider the feedback over the next two months as we review our policy. We have certainly no intention of lowering our standards on conflicts of interests, but we are open to further improving our approach.

When reviewing the policy, we must also look to the future. I am of the view that we also need to think about the methodology going forward. We need to recognise the changes that will be necessary, given the anticipated increase in the area of advanced therapy medicines, and the potential for a corresponding decrease in the number of available experts.

In closing, I would say that in revising the EMA's conflicts-of-interests policy we will have to balance the views of those who believe the policy is not strict enough with those of others who say it is too strict, and find a perfect place somewhere between the two."

Guido Rasi, Executive Director

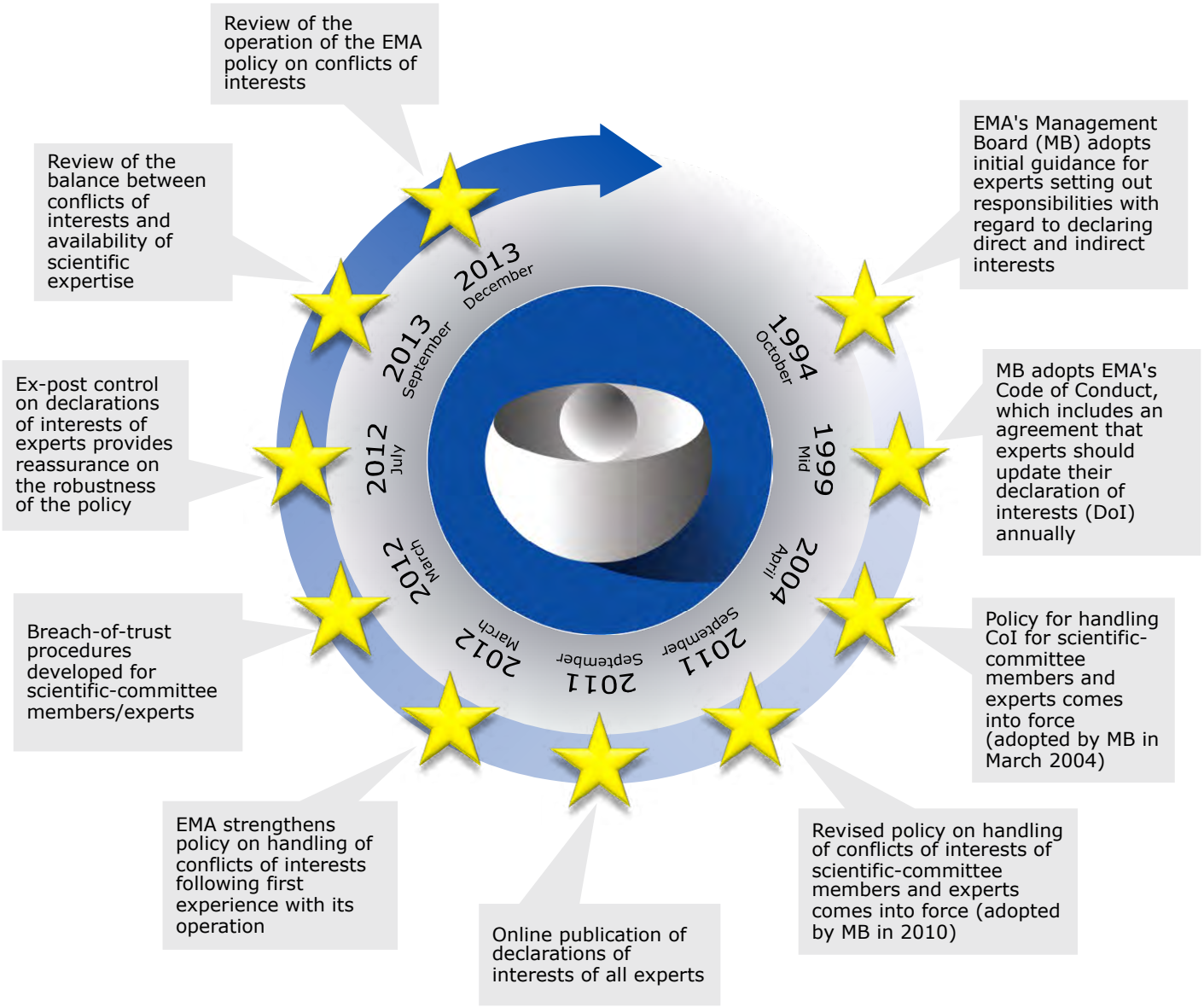
Guido Rasi wrapped up the workshop by thanking participants for taking part. In his closing remarks, he said that one approach could be to define a methodology for identifying the best expertise within the EU. He proposed that another solution when considering potential conflicts of interests could be to move away from blanket timeframes (e.g. within the past two years, within the past two to five years or over five years), towards an approach that first looks at the nature of the interest before determining how long it takes for the interest to be over.

Next steps

Inputs from the workshop will now be considered by the Agency as it moves into the revision cycle of its policy on conflicts of interests. It is anticipated that proposals will be presented for discussion at the Agency's Management Board in December 2013.

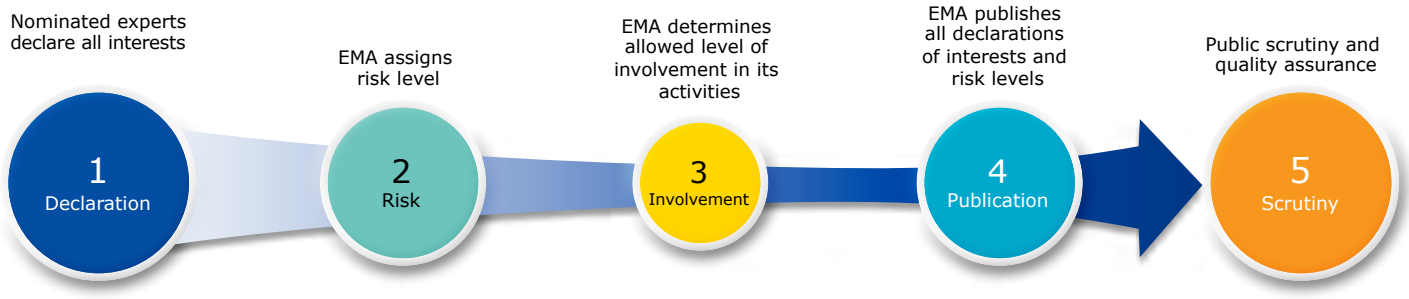
Historical overview: conflicts of interests at the European Medicines Agency: actions and ongoing initiatives

The European Medicines Agency has, since its creation, continuously strengthened its handling of conflicts of interests, taking into account lessons learned. The graphic below offers a snapshot of key milestones achieved between 1994 and 2013.



The process for involvement of experts in EMA activities

Once the scientific experts have been nominated, there is a five-step process that needs to be followed before they can become involved in any EMA activity.



Step	Action	Notes
One	Nominated parties must declare all interests	The declaration of interests must include information about any direct and indirect interests. Experts must declare their interests at least once a year
Two	EMA assigns the expert a risk level	The risk level assigned (1, 2 or 3) reflects the nominee's declared interests, both direct and indirect. Levels of risk are governed by set timeframes, such as employment or consultancy at a pharmaceutical company, within the past 5 years
Three	EMA uses the risk level to determine an expert's permissible level of involvement in Agency activities	After assigning a risk level, the Agency uses the information provided to determine whether an expert's involvement in a specific EMA activity is possible or should be restricted. It bases this decision on the nature of the interests declared (direct or indirect), the time since the interest occurred, and the type of activity that the expert will be undertaking
Four	All declarations of interests and assigned risk levels are published	To maximise transparency, all declarations of interests and assigned risk levels relating to its experts are published online
Five	Public scrutiny and quality assurance	Publication of the Agency's experts' interests and risk levels allows for public scrutiny of this information

Related information

An overview of the EMA's policy on conflicts of interests for scientific-committee members and experts is available in the separate document 'At a glance' (EMA/546668/2013).

For brief biographies of the panel members of this workshop, see 'Speaker profiles' (EMA/544803/2013).

Further information on the Agency's handling of conflicts of interests is available on its website here.

European Medicines Agency

7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

Telephone +44 (0)20 7418 8400
Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu

www.ema.europa.eu

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