



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## **EMA-HTA workshop**

Bringing together stakeholders  
for early dialogue in medicines  
development

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Report from the public workshop hosted by the European  
Medicines Agency (EMA) in London on 26 November 2013



## Executive summary

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"Strong interaction between regulators and health technology assessment bodies (HTAs) is critical to enable innovation to reach patients, and ultimately for the benefit of public health. This is the first workshop where we have tried to bridge these two worlds together to share views," said Guido Rasi, Executive Director of the European Medicines Agency (EMA).

In November 2013, the EMA hosted a landmark workshop to look at the need for, and the current use of, parallel scientific advice from regulatory and HTA bodies during the medicines development process.

Since 2010, the EMA has established a pilot project of parallel scientific advice with HTA bodies that allows developers to receive simultaneous feedback from both regulators and HTAs on their development plans for new medicines.

The objective of the workshop was to discuss lessons learned, and ways to optimise the process of parallel scientific advice. The workshop brought together over 280 representatives from, among others, the European Commission, European regulators, HTA bodies, EUnetHTA, the industry, payers, patients and healthcare professionals.

### Why is EMA/HTA parallel scientific advice needed?

A number of new medicines authorised by the European Commission based on the EMA's scientific opinions are either not reimbursed by national health systems and/or used as expected because they do not match the requirements of HTA bodies. Therefore, there is a clear need to initiate early dialogue between medicines developers, the EMA and HTA bodies to discuss and agree upon development plans that generate data that both parties can use to determine a medicine's benefit-risk balance and value. This would ultimately facilitate the development of safe, efficient and affordable medicines with real therapeutic added value, equally available for all patients in the European Union (EU), and reduce delays to patient access to medicines.

## Lessons learned

At the workshop it was acknowledged that EMA-HTA parallel scientific advice is necessary to learn about HTA requirements at an early stage in the medicines development process, and to minimise divergent data requirements between regulators and HTAs, and between participating HTA bodies.

Stakeholders recognise that different frameworks drive the data needs for regulators and HTA bodies. To facilitate more efficient data collection, there is a need to reconcile and align data requirements where possible, or to compromise on data needs if data alignment is not possible. Methods are needed also to address remaining potential divergences.

It was also acknowledged that understanding the perspectives of different stakeholders at an early stage promotes mutual understanding and ultimately leads to better scientific advice. Mechanisms are needed to help medicines developers integrate these different views and, in particular, to bring the patient perspective to the heart of the decision-making process.

## Next steps

There was strong support from all stakeholders for parallel EMA-HTA scientific advice and simultaneous feedback. Industry representatives see the need for optimising the procedure with process guidance, clear ownership, HTA engagement, clear HTA outputs, expertise in meetings, procedure flexibility and streamlining.

Based on the experience gained by all stakeholders, guidance for EMA-HTA parallel scientific advice is under development and will be published for public consultation in May 2014. This guidance will be an important tool for medicine developers.

## 1. Introduction

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In November 2013, the EMA hosted a workshop to look at the need for, and the current use of, parallel scientific advice from regulatory and health technology assessment (HTA) bodies during the medicines development process. The workshop brought together over 280 representatives from, among others, the European Commission, European regulators, HTA bodies from 12 EU Member States, the European Network for Health Technology Assessment (EUnetHTA), the pharmaceutical industry, payers, patients, healthcare professionals and academics. Also present were regulatory representatives from the Committee on Medicinal Products for Human Use, the Pharmacovigilance Risk Assessment Committee, the Paediatric Committee, the Committee for Advanced Therapies, the Committee for Orphan Medicinal Products and the Scientific Advice Working Party. A further 200 members of the public across more than 23 countries accessed the event via a live webcast.

Delegates were asked to look at a wide range of issues relating to parallel regulatory/HTA scientific advice, focusing on the EMA-HTA parallel advice pilot process in place since 2010. Other current and future options were also considered, such as the 2013 early dialogue pilots through EUnetHTA with HTA bodies alone and forthcoming developments including the SEED (Shaping European Early Dialogues) initiative. The issues included:

- why there is a need for parallel scientific advice between regulators and HTA bodies;
- what are the possible aims for future parallel scientific advice between regulators and HTA bodies;
- lessons learned so far scientifically and procedurally from the ongoing EMA-HTA parallel scientific-advice pilot project;
- how the process can be moved forward to meet these aims through engagement of all stakeholders.

Opening the meeting, EMA Executive Director Guido Rasi told delegates that a "strong interaction between regulators and HTA bodies is critical to enable innovation to reach patients, and ultimately for the benefit of public health. This is the first workshop where we have tried to bring these two worlds together to share views. We hope to build a strong and permanent bridge between regulators, HTA bodies and payers with these aims in mind."

Rasi added that the sheer number of participants in the room representing countries across the EU and beyond was a testament to the need for change. "We have to reduce drug development time. We are bound to try any approach we can to reduce that timeline, such as running processes in parallel rather than in sequence. Scientific advice with regulators and HTA bodies is just one example of where this could happen more."

During the meeting, it became clear that every stakeholder involved in the medicines development process has a genuine desire to work together in order to establish an ethos of seeking and delivering parallel regulatory HTA scientific advice. All stakeholders agreed that developing a clearer understanding of each other's needs and seeking ways to better align or address these needs, would in the end bring more benefit to patients.

## 2. Why is EMA/HTA parallel scientific advice needed?

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A number of new medicines authorised by the European Commission based on the EMA's scientific opinions are either not reimbursed by national health systems and/or used as expected because they do not match the requirements of HTA bodies.

There is a clear need to initiate early dialogue between medicines developers, the EMA and HTA bodies to discuss and agree on a development plan that generates evidence that both parties can use to determine a medicine's benefit-risk balance and value.

Examples of difficult and lengthy health technology appraisals were referred to by David Barnett, Emeritus Professor of Clinical Pharmacology at University of Leicester, and Chairman of the Appraisal Committee for the National Institute for Health and Clinical Excellence (1999-2009). These included Lucentis for wet age-related macular degeneration, beta interferon for multiple sclerosis and antiTNF agents in psoriasis. It can be asked whether these appraisals could have been different if early dialogue with HTA bodies and regulators had been available to optimise the nature or extent of data gathered throughout the development programme.

The impact of multiple divergent data requirements on the development of a new medicine was shown in an industry case study highlighted by Britta Paschen, Head of Global Health Services Research at Merck Serono. She indicated that concerns and possible implications of receiving conflicting advice from regulators and different HTA bodies was a real concern for companies.

From the outset, we decided that where the feedback advice from regulators and HTA bodies was contradictory, we would follow the advice of the regulatory authorities worldwide," said Paschen.

"The choice of the comparator has been very difficult and, in this indication, different patient populations may be treated differently. Furthermore, other older therapies have become a standard of care without a broad evidence base and without a licence in this case study. In terms of dose, for example, there was varying feedback in the risk/benefit ratio of the dose and selection of the dose. When it came to clinical trial inclusion criteria, there was tension between standardisation on the one hand and clinical practice on the other. We had to look at how homogeneous or diverse the patient population in the pivotal trial should be. In fact, inclusion criteria also played an important role for indirect comparisons too. We had to consider the inclusion criteria of comparators and their clinical trials in order to prepare for indirect comparisons," Paschen added.

In addition to the differences between regulators and HTA bodies, it was evident that divergences also exist between HTA bodies themselves in terms of information needs. Indeed, the differences relating to the scientific criteria used to assess a product and different evidence demanded by the various HTA bodies is seen as a key hurdle in the current environment. These wide-ranging criteria include comparators (licensed and unlicensed), endpoints and surrogates.

With regard to HTA bodies, "comparative efficacy and effectiveness is very important for the payer," added David Barnett.

In fact, in the measurement of effectiveness, the choice of comparator was one of the issues that delegates felt most apprehensive about when it comes to health technology assessment, with very few HTA bodies accepting the same comparator, agreeing on alternatives or aligning their request with that of regulators.

Whilst assisted by the regulatory scientific advice process, many industry representatives remain concerned about the lack of clarity and consistency surrounding the data being sought by the different HTA bodies. "I think we are in a good place with regulators. We have open dialogue and mutual respect. We now need a similar dialogue with payers. We cannot go on having more than 28 approaches to assessing therapeutic value across Europe," said Richard Bergström, Director General of the European Federation of Pharmaceutical Industry Associations (EFPIA).

Bergström suggested that being in the same room as other stakeholders and able to listen to each other's points of view, may result in HTA bodies, for example, potentially changing their opinions or decisions. At the very least it could foster an alignment of understanding, which would enable companies to design a global development programme that meets the requirements of regulators and HTA bodies from the outset.

The situation is further complicated because the healthcare industry is shifting from a blockbuster model to one that is seeing an ever-increasing reliance on targeted medicines. By their very nature, these targeted medicines have a smaller patient population, which means that the data being asked for by regulators and HTA bodies is more complex to gather and therefore has to be used efficiently. Developers have to balance these divergent information requirements on one hand with the potential constraints of a global development programme on the other. The development of new medicines is a long term process and represents a huge investment for developers who need to make conscious, informed decisions to reduce risk and uncertainty in the outcome.

In 2010, the Agency launched a pilot project of parallel scientific advice with HTAs that allows developers of new medicines to get simultaneous feedback from both regulators and HTAs on their development plans. So far, the project has proved to be a success: with the support of the European medicines regulatory network, the EMA had conducted 25 parallel scientific advice procedures by the end of November 2013 (covering indications such as diabetes, mesothelioma, multi-resistant infections, and Alzheimer's disease) with several HTAs taking part. Currently, a further six procedures are expected to start in 2014.

## Why is EMA-HTA parallel scientific advice needed?

- To learn about HTA requirements at an early stage
- To minimise divergent data requirements between regulators and HTA bodies
- To address divergent data requirements between participating HTA bodies
- To reduce delays to patient access
- To facilitate medicines development in the current climate of economic constraints on healthcare budgets, with greater implementation of HTA and reimbursement approaches
- To contribute to managing increased medicines development costs
- To help to address the constraints of global medicines development programs
- To contribute to managing shifts in healthcare industry such as targeted medicines with niche population and orphans diseases

## 3. Where do we want to get to?

Yann Le Cam, Chief Executive Officer at EURORDIS, clearly evoked the patients' interest: to achieve the quickest access to as many safe, efficient and affordable medicines with a real therapeutic added value, for patients in the EU.

This common goal can only be delivered by all relevant interested parties working together, each addressing their respective elements in a coordinated fashion, he said. Le Cam appealed for more dialogue between regulators and HTA bodies, including very early discussions, a more integrated HTA view and greater patient involvement: "The European Commission shared the view that we are entering a new era in EU-HTA cooperation and defragmentation where we can build on synergies between HTA bodies and regulators and that work has started to support this at strategic and scientific levels."

With a fundamentally changing global pharmaceutical environment, dialogue between industry and payers is even more essential – it could expand on the well-established process of dialogue with regulators. While there are many ongoing initiatives with this goal in mind, alignment and involvement of the EMA and the European Commission is recognised by many as a vital component. Furthermore, simultaneous feedback from regulators and HTA bodies is needed both pre- and post-licensing.

In principle, understanding the differences in evidence requirements for each stakeholder through parallel scientific advice would be extremely valuable, as would facilitating ways both to respond to these differences and to overcome obstacles to determining value, even if agreement and uniformity of approaches cannot be settled upon.

Crucially, regulators and HTA bodies must engage in this process addressing their respective roles and responsibilities. Simultaneous engagement to achieve a common development track for new medicines must not simply settle on the highest 'common denominator' but rather an optimised approach though consensus and compromise.

Regulators are well aware of the demands that they place on companies but are clear that, in the end, it should be a win-win situation. Rob Hemmings, chair of the EMA's Scientific Advice Working Party and medical statistician at the UK's Medicines and Healthcare products Regulatory Agency (MHRA) said: "We must guard against confusion with roles and responsibilities. At the same time we need to ask ourselves which HTA needs we are trying to align ourselves with. This can be hard to say. Therefore, there is a need to concentrate on collecting the right data in an efficient way to inform everyone's different needs.

"From our experience in the pilot programme, there is definitely an open mind towards the idea of changing and enhancing the confirmatory development programme so it also meets the needs of the HTA bodies. If that means compromising on an unimportant parameter usually requested in a regulatory guideline, then so be it.

It is harder to compromise on key methodologies that are essential to minimising bias, potential for bias or the potential for false positive errors. In addition, if there are divergences between HTA bodies, how are these compromises rationalised?"

## Where do we need to get to with EMA-HTA parallel scientific advice?

- Facilitate the development of as many safe, efficient and affordable medicines – with real therapeutic added value – that are available to all patients across the EU
- Increase early dialogue between different stakeholders
- Understand the differences between, and perspectives of, different stakeholders
- Increase patients' involvement
- Contribute to the alignment of different HTA views through parallel EMA-HTA scientific advice discussions
- Respect the roles and responsibilities of all stakeholders
- Explain and encourage wider uptake of the scientifically-binding approach in the provision of advice
- Maximise efficient resource utilisation to avoid duplication

## Patient power and opinion

- With all stakeholders agreeing that patients should have a seat at the table, delegates at the EMA/HTA workshop were given the patient perspective by Yann Le Cam, from EURORDIS. "Our overall objective has remained unchanged – to achieve the quickest access to as many safe, efficient and affordable medicines with a real therapeutic added value, for all rare disease patients in the EU," he stated. "We need to bridge the gap between the EU centralised regulatory decision and the national decision on pricing and reimbursement," he added.
- EURORDIS would like to see regulators and HTA bodies becoming partners, moving beyond quality, safety and efficacy to focus on effectiveness throughout a product's development. This would require early dialogue between regulators and HTA bodies at the very least or, even better, a conversation on clinical trial design that includes, sponsors, medical experts and patient representatives. "We need to move away from the individual HTA model towards an EU-wide network of HTA bodies that involves patients as experts not just observers. However, this will mean we need to have a common understanding of what value actually is," added Le Cam.
- To make the process and requirements clearer, Le Cam suggested that the EMA and HTA bodies consider developing a set of guidelines for specific diseases or groups of diseases in terms of clinical trial design.
- Richard Bergström, from EFPIA, was clear that patients are increasingly important in medicine development. He reminded delegates that 20 years ago companies did not talk to the regulators but now it is standard practice. New stakeholders need to be included in the development process, namely patients. "There is still a way to go on the industry side in terms of listening to patients in earnest when designing programmes," he commented.
- David Barnett agreed that patients should be involved, pointing out that both patients and carers are best placed to offer meaningful feedback in terms of HTA markers such as quality of life. Patient-reported outcomes may also need to be considered much earlier in the development process.
- At the same time, many speakers, whilst agreeing that patients must be more involved in the process, warned against increasing the burden already placed upon them.

## 4. Key themes from the workshop

### At a glance: what regulators and HTA bodies consider

#### Regulators

- Safety
- Quality
- Efficacy
- Risk/benefit

#### HTA bodies

- Efficacy - does it work in clinical trials?
- Effectiveness - does it work in clinical practice?
- Efficiency\* - does it contribute to more efficient use of resources?

\*Not all HTAs

Mel walker, Vice President of Market Access at Otsuka Pharmaceutical Europe framed the session on 'Accommodating the scientific needs of regulators and HTA bodies in a common development track' with three questions:

1. What are the potential areas for alignment and where will it be difficult to align parameters whilst recognising that artificial alignment may come at a cost of eliminating strategic options for product Phase 3 programmes?
2. What is the right balance between the perfect experiment and ideal real-world scenarios? How do we balance the need to broaden trials to make them more pragmatic with the need to keep the trials tightly designed? Should we be looking for alternative ways to gather real-world data?
3. What mechanisms could help medicine developers make sense of the various perspectives held by stakeholders and improve their understanding of how to integrate these different perspectives? Would a better understanding of the framework that different stakeholders are using to drive their decision making and placing the patient perspective at the heart of that process help?

During the event, participants were reminded of the decision-making framework respectively for regulatory and HTA bodies, and consequent information needs of the regulators and HTA bodies (see above box: At a glance: what regulators and HTA bodies consider).

### The regulatory view

In assessing efficacy and safety, Rob Hemmings reminded delegates that regulators are interested in the medicinal product in question, its therapeutic effects and its harms, not in the overall healthcare system. Regulators base their decisions for licensing almost exclusively on randomised controlled trials that attempt to give a clean answer to a clean question. The database that is generated to support the evidence presented by the applicant is available, can be verified, and interrogated to assess the robustness and standards of the trial and data collection. A more uniform controlled trial gives trial results that are likely to be clearer avoiding biases. A more 'real world' pragmatic trial may be open to more generalisations, but is at increased risk of introducing bias and uncertainty.

The challenge is to strike the right balance when considering trial design elements such as population criteria for inclusion, clinical outcomes, and between general and targeted patient reported outcomes. The choice of comparator is critical. Regulatory authorities have a duty to ensure that the evidence of efficacy is convincing, and that the degree of efficacy is sufficiently substantial to outweigh any safety risks or problems with side-effects, relying heavily on robust evidence. Regulators consider that straightforward randomised placebo-controlled comparisons are generally scientifically desirable for reliable evidence of efficacy, even when active treatments are already in widespread use. Where a placebo control is not possible, such as when efficacious treatments are available and placebo places the patient at an unacceptable risk of irreversible harm, an appropriate active comparator should be used.

### The HTA view

In contrast, given that HTA bodies are interested in populations and comparators representative of local conditions, Leeza Osipenko, Senior Scientific Adviser for the UK's National Institute for Health and Care Excellence (NICE) encapsulated NICE's needs; "So how well does it work in clinical practice and is your product worth being reimbursed? What you need to demonstrate to the payer is the value of your product. You need to show how much better it is that what the patients are getting now, you need to show that the price is justifiable, you need make sure the evidence you present is robust and of good quality."

Osipenko acknowledged that comparators are often the cornerstone of controversy between HTA bodies and regulators, let alone amongst HTA bodies themselves. Nevertheless, she urged developers to seek advice in the first instance. "We are very supportive and interested in active comparator trials and we think there should be wider support across the board. However, we do understand there are restrictions. Sometimes these are not possible or not pragmatic to conduct. We understand the requirements you face from the regulator but we need to know about these issues. We are prepared to work with you to take all these requirements on board, to help you make indirect and mixed treatment comparisons and to advise you on the best use of evidence to support the case for health technology assessment," she said.

On the subject of endpoints which can also be a point of divergence, Osipenko said "from the HTA perspective, if you use surrogate outcomes in your trial, it is very important to prove the relationship of the surrogate to the final outcome. Quality-of-life data are very important [to HTA bodies] and should be collected in the trial with the aim to get utility values in countries that would need them." Whilst HTA bodies usually prefer generic measures for quality of life, selection of disease specific measures have been frequent topics of discussion in parallel scientific advice.

Other ideas raised in the workshop to bridge data divergences included increasing sample sizes, use of pre-specified subgroups, extrapolation methods, modelling or post approval data collections.

For HTA bodies, the roles of active comparator, capturing the main cost drivers, the importance of the whole care pathway, long term horizons and the local perspectives of the decision makers, additional data for the economic model (costs, resources, epidemiological data) and qualitative parameters (legal/ethical aspects of the technology patient experiences and preferences) were also highlighted together with the impact of innovation, end-of-life care and the extent of uncertainty.

The HTA representatives believe that the key to success is to start thinking about potential requirements early on and to ensure the value proposition of a product matches the clinical trial programme. "Planning and incorporating the requirements into your clinical development programme will help you reach reimbursement much sooner and much closer to the market authorisation of the product," said Osipenko.

Regulators and HTA bodies at the workshop were open to engaging with each other on a scientific level and considering how to build the information needs of HTA bodies into confirmatory clinical trials to minimise the timeframe between the marketing authorisation and reimbursement decisions. Stakeholders acknowledged the need to avoid placing excessive burden of additional assessments on patients.

## Lessons learned so far in EMA-HTA parallel scientific advice – the science

- Stakeholders do recognise that different frameworks drive the data needs for regulators and HTA bodies
- Mutual understanding amongst stakeholders can lead to better scientific advice
- Stakeholders can aim to reconcile, and align, data requirements where possible
- Stakeholders can endeavour to compromise on data needs if data alignment is not possible
- More efficient trial data collection is needed
- Methods to address identified divergences are needed
- It is important not to gold plate development programmes
- The burden on patients taking part in trials should not be increased
- Stakeholders already recognise common good scientific methodological principles and synergies

## Scientifically binding advice

During the EMA's workshop, many of the stakeholders referred to the advice as not being legally binding, but suggested that it should be scientifically binding on the applicant and the regulatory authorities. The EMA views scientific advice to be scientifically binding when:

- Regulators give scientific advice based on the current state-of-the-art in medicine development
- Regulators recognise that in some cases, e.g., as a result of scientific developments, an alternative approach to that advice may be appropriate
- However, where companies choose not to apply the advice, they are requested to justify clearly their position in any subsequent marketing authorisation application
- Likewise, regulators will provide argumentation during the evaluation of the marketing authorisation application in the rare case of diverging from its position in scientific advice

## 4.1. What has been learned procedurally?

The EMA regulatory scientific advice model has evolved in scope and capacity over more than ten years and is fundamentally dependent on the interaction and contribution of delegates from national competent authorities to produce an EU regulatory scientific consensus advice. EMA-HTA parallel scientific advice dovetails into this existing procedure to enable the EMA advice to be given. HTA bodies engage with this adapted procedure but give their own advice in parallel to regulators on the questions that have been proposed by the company and based on supporting information.

### EFPIA/EuropaBio survey results

To examine the success of the various pilots already undertaken, EFPIA and EuropaBio each carried out surveys. "The EFPIA survey revealed that all 23 companies that responded agreed that parallel advice would be good and the majority of respondents indicated that they would prefer to use the EMA-HTA approach. In fact, seven of the companies have already used this system," explained Christine Mayer-Nicolai Senior Director, Global Regulatory & Scientific Policy at Merck Serono and EFPIA.

Respondents reported that witnessing the engagement between regulatory and HTA representatives in the same room was very valuable. They also reported that, from a company perspective, getting clarity on areas of consensus and divergence means the company can better understand what changes it has to make and where it might need to consider so-called 'trade-offs'.

Feedback from the survey shows that the confidential and non-binding parallel advice process needs to be informed, specific, timely and fit for purpose. It is also clear that the process must be evaluated and must evolve as the uptake increases.

The National Institute of Clinical Excellence (NICE) led the way in the number of EMA-HTA parallel scientific advice procedures undertaken, taking part in ten. This was followed by Germany and Italy who both undertook six. While eight companies indicated that they would take part in a scientific advice procedure in the coming two years, 13 remained unsure. None, however, stated that they would not take part in the future.

Feedback on the HTA-only early dialogue procedures was equally as positive with companies reporting that the time allotted to the meeting allowed for meaningful dialogue to take place.

Meanwhile, the EuropaBio survey revealed that small and medium-sized enterprises (SMEs) are not yet actively seeking parallel EMA-HTA scientific advice. "The majority of respondents stated that they did not think the system would be flexible enough to meet their needs and that they do not have the capacity to fulfil the perceived requirements," said Paolo Morgese from EuropaBio. Solutions are therefore needed to help SMEs engage further.

From feedback received on both the surveys, it is clear that further work needs to be done to disseminate more information about the process design and the ease of the procedure as a whole.

## How does the parallel scientific advice process work?

Feedback from participants at the workshop indicated that the current parallel scientific advice process being spearheaded by the EMA and HTA bodies is very simple and sets out clearly what each of the stakeholders needs to do at each particular point. Following a letter of intent, which is sent to both the EMA and participating HTA bodies, the company prepares and sends out the common draft of a briefing document or 'book'. Following a conference call and amendments made from feedback, the final version of the briefing book is issued. Once that has been circulated and assessed, there is preparatory conference call between HTA bodies and regulators to identify issues. Then the scientific advice meeting takes place between all stakeholders. The minutes of this meeting are also circulated.

## Some issues to address

There is a need for a sustainable process with clear ownership and guidance, with predictable HTA participation and a clear HTA advice output according to Mayer-Nicolai from Merck Serono and EFPIA. Process flexibility was also desirable while more than one advice platform may be required to suit different applicant requirements.

All delegates agreed that there was a need for a more defined process for seeking scientific advice from HTA bodies, and that the advice must be sought as early as possible – preferably at the same time that companies are seeking advice from regulators. It is clear that every stakeholder agrees there would be a real benefit from having both regulator and HTA in the room at the same time when questions were being answered and advice offered.

Jan Mueller-Berghaus from the EMA's Scientific Advice Working Party and CHMP member agreed that the sheer number of people in the room has its advantages. Using the example of

the Scientific Advice Working Party, he said: "Having all these people in one room, while contradictory remarks might be expressed, it is good to exchange views. In the end you will have a harmonised EU regulatory view. You may not like it but at least it is a creature you can deal with and work with in the future."

In fact, Seren Phillips, former Associate Director for the NICE Technology Appraisals Programme believes that the existing machinery of the EMA has made it easier for the HTA bodies to join in because the process itself is already established. She said the meeting offers "a really valuable opportunity to hear the views and reasoning of both regulatory agencies and other HTA bodies". She acknowledged the need for dedicated resources and planning for capacity building together with calls for formal exchanges on outputs between regulators and HTA bodies. However, given the overall lack of clarity and the amount of confusion that pervades the current HTA system, it is clear that steps need to be taken to develop a process based on EU-wide principles and agreed scientific standpoints.

## Lessons learned so far for EMA-HTA parallel scientific advice – the process

- There is strong support from all stakeholders for parallel EMA-HTA scientific advice and simultaneous feedback
- Feedback from HTA bodies suggests that the process is easy to join in
- Industry sees the need for optimising the procedure with process guidance, clear ownership, HTA engagement, clear outputs from HTA bodies, expertise in meeting, procedure flexibility and streamlining
- SMEs are concerned about resources needed and complexity of the HTA environment
- HTA bodies will need dedicated resources to meet the challenge of building capacity and a formal exchange of outputs

## 4.2. Moving forward

To come up with some potential solutions to the hurdles of early dialogue and joint meetings, delegates at the workshop split into groups to look at the issues in more detail. They focused on four key areas:

- Principles and policies
- Science and data
- Process and procedures
- Special interest areas.

## Principles and policies

The group tasked with examining the principles behind the move towards joint meetings and early parallel advice, agreed that such meetings should always keep in mind that they are working towards improving public health by delivering safe and effective medicines to patients. The group suggested that in areas such as the choice of comparator where consensus is not possible, there should be a recognised mechanism for compromise. This should be supported by a clearer decision-making pathway to drive a better understanding of the acceptable trade-offs in the development programme. The development of guidelines might make this mechanism easier to establish, suggested the group. A one-off scientific discussion might not be sufficient; parallel EMA-HTA scientific advice could be invaluable in managing the lifecycle of a product which means ongoing dialogue.

There also needs to be greater clarity when it comes to identifying the actual decision makers and whether they are the ones offering the advice. If they are not, then there needs to be more information about how the decisions will be made. Finally, everyone at the table agreed that in terms of predicting needs, involving patients and physicians will only improve this.

## Science and data

Tasked with looking at ways to meet different needs when it comes to elements such as comparators and endpoints, the second group at the workshop accepted that there needs to be further debate and discussion to really get to a point of compromise – a debate that could not happen on the day. From the outset of the discussion, it was obvious that there is a need for the dialogue between developers and HTA bodies to start even earlier than it does now and for agreement on common assessment parameters.

They suggested that as the industry moves beyond classical data-gathering techniques, it will need to develop new systems to ensure the data that are being captured are suitable. However, it also asked if HTA bodies need to be more flexible when it comes to the data used in areas of high unmet medical need and whether developing set methodological principles would help the whole science-based process.

Finally, while they agreed that there is a need for more patient involvement, the group expressed concern about adding to the burden of patients by asking them to report outcomes.

## Process and procedures

The group tasked with working on the actual process when it comes to early scientific advice took the current process used when seeking scientific advice from the EMA HTA parallel scientific advice and looked at how it could be optimised based on the feedback received.

When undertaking HTA advice, companies first need to uncover the individual requirements from the different HTA bodies. The group suggested that this data could be collated and published online. They also questioned why, given they have had conversations and submitted the briefing book, companies could not get feedback about the emerging divergences between different stakeholders before the face-to-face meeting so they could start to prepare and consider how to address the critical issues. Finally, they proposed setting up a possible feedback and follow-up mechanism.

## Special interest areas

When dealing with orphan medicines, advanced therapies and personalised medicines, developers face significant issues, especially in terms of small target populations and even a lack of awareness about a disease. The group agreed that the science, process and policy behind reimbursement decisions all needed to be examined more closely. They suggested that decision makers need to make use of an existing network of experts and that where they exist, HTA bodies should review EMA guidelines when looking at products. Parallel broad advice and qualification procedures were suggested. Knowing if value might be attached to the development of a new medicine or if decision makers are unlikely to be willing to pay for technology where there is limited added benefit is even more important in the rare disease arena. Long-term data collection post authorisation concerning the effects of the therapy could be informative.

## 5. Next steps

Guidance for EMA-HTA parallel scientific advice is now being developed and a draft will be published for public consultation in 2014 in collaboration with stakeholders. The guidance will outline the timelines and actions whereby applicants can seek simultaneous feedback from regulators and HTA bodies on their product development plans. The guidance will take into account feedback from all stakeholders. Thus EMA-HTA parallel scientific advice as undertaken in the pilot is set to continue and evolve. Scientific advice/early dialogue involving regulators and HTAs is now identified as an area of collaboration under the EMA-EUnetHTA three-year work plan 2013–2015.

Wrapping up the workshop, Tomas Salmonson, Chair of the Agency's Committee for Medicinal Products for Human Use, said: "I believe that this guidance can be a major tool for medicines development, which will help new medicines with a positive benefit-risk balance and expected added value to reach patients in a faster and more transparent way. This simultaneous feedback will ultimately lead to better advice for companies, to help them meet the requirements of all stakeholders and consequently increase predictability."

Furthermore, 14 national and regional HTA bodies have initiated a new project known as the Shaping European Early Dialogues for health technologies (SEED) consortium. Financed by the European Commission and led by French Haute Autorité de Santé, SEED will explore a number of scenarios for conducting early dialogues. SEED will perform ten multi-HTA early dialogues (seven pharmaceutical products and three medical devices) covering key aspects of their development and identifying specific HTA needs related to the relative effectiveness and cost-effectiveness assessment. The EMA will undertake three parallel regulatory SEED procedures as part of this initiative with the consortium. SEED consortium members are also partners in the EUnetHTA Joint Action 2.

Moving forward, it is clear that all the stakeholders involved in seeking and giving scientific advice and holding early dialogue meetings see the benefits and want to streamline the process. "There is an appetite for joint advice. We all agree early dialogue is important. If we can agree on a common methodology on how best to address these differences that would indeed be a start," said Salmonson.

## 6. Appendices

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### Definitions

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#### Joint meetings

A meeting where both regulatory body representatives and HTA representatives are present and willing to answer questions posed by a company.

#### Parallel scientific advice

A system whereby regulatory bodies and HTA bodies issue advice at the same time rather than sequentially.

### History of HTA early dialogues

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In 2005, recognising the need to establish a sustainable European network of HTA bodies, the European Commission (EC) oversaw the setting up of the EUnetHTA Project, a network of HTA bodies with the objective of working together in order to develop reliable, timely, transparent and transferable health technology assessment scientific information across Europe. The project facilitated a number of work packages leading up to the Joint Action 1 in 2010, which set out to develop principles and methodological guidance alongside functional online tools and policies. HTA bodies have performed several multi-HTA-body early dialogues within the framework of the EUnetHTA Joint Actions 1 and 2, and the EMA was invited to participate as an observer in the multi-HTA-body early dialogues of EUnetHTA Joint Action 2.

The EC also established the HTA Network, a voluntary initiative that brings together the competent authorities responsible for health technology assessment. "All Member States have appointed a representative and the network held its first meeting at the end of 2013 to host a strategic discussion on European collaboration when it comes to health technology assessment. The HTA Network will be supported by a scientific and technical cooperation mechanism, a function which will be fulfilled by Joint Action EUnetHTA until the end of 2015," explained Flora Giorgio, Scientific Officer at Commission.

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