Parallel EMA–HTA advice: **Past, present, and future**

Dr Jane Moseley, Senior Scientific Officer, Product Development and Scientific Support Department (Scientific Advice) at the EMA, spoke to **Julie Warner** *and* **Anita Sibal** *on her experience as EMA lead on the parallel EMA–HTA advice initiative*

Q: Can you tell us a bit about your background and what your main responsibilities are at the European Medicines Agency [EMA]?

A: I am a medical doctor by training, and completed my degree at Trinity College in Dublin, Ireland, before specialising in ophthalmology and epidemiology. I spent ten years working at the UK's Medicines and Healthcare Products Regulatory Agency [MHRA] before joining the EMA about five years ago.

My current role is as a member of the Scientific Advice team at the EMA, and my responsibilities include project management of both standard scientific advice and parallel EMA–HTA [health technology assessment] advice procedures in certain therapeutic areas including ophthalmology. At the end of 2013, I organised the EMA workshop on parallel EMA–HTA advice and led the initiative for the Best Practice guideline (issued in May 2014) and its regulatory–HTA working group.

I also have other responsibilities, including the PRAC–SAWP [Pharmacovigilance Committee/Scientific Advice Working Party] interaction process initiative, the Post-Authorisation Efficacy scientific guidance and recently I organised a regulatory workshop on clinical trial design in neuromyelitis optica and spectrum disorders. There is a very high unmet medical need in this rare and debilitating condition. In the face of widespread use of unlicensed treatments based on sparse data, there are divergent views among regulatory agencies about whether registration trials can be placebo-controlled or not. Patients were involved in the workshop, and it was very interesting and highly motivating to have such a workshop to try and facilitate drug development.

Q: What were your initial thoughts when the EMA started to work more closely with HTA bodies to derive a process to ensure efficient access of patients to novel products, and what did you think the biggest challenge would be when you saw its scope?

A: Firstly, we welcomed this initiative as a way of moving drug development forward to facilitate patient access to medicines. It was widely acknowledged that neither the EMA nor the HTA bodies could achieve this on their own. The Commission was also aware of the need and put in place initiatives like SEED [Shaping European Early Dialogues], to facilitate the synergies. At that time, there had been no parallel advice procedures with HTA bodies and, as such, it was necessary to consider the needs of all stakeholders and be sensitive to how things could play out. All parties needed to feel equally respected and engaged. The EMA's scientific advice procedure had existed for some time, and companies and regulators were familiar with the process. HTA is a process much closer to pricing and reimbursement decisions and therefore HTA bodies are much more dependent on national procedures and approaches, and there are more players (HTA bodies themselves, the payers, and patient groups). This was a challenge in itself.

Q: Could you describe your contribution to, and experience with, the EMA–HTA parallel advice pilot?

A: I was involved in several of the EMA–HTA parallel advice pilots on specific products, working up the initial procedure together with HTA body representatives. We are also now reviewing the comments received from the public consultation of the Best Practice Guide on parallel EMA–HTA scientific advice and thinking about how we can further optimise the procedure.

Regarding the SEED initiative, I have been involved in designing an initial common EMA SEED procedure together with SEED partners. We are gaining experience with every procedure and also considering how to move this forward.

Q: Did anything surprise you during your participation in the EMA–HTA pilot procedures? What have been the key learnings and challenges to date?

A: I am pleased to see lots of positivity during the pilot procedures for parallel engagement by all stakeholders at the advice stage.

The biggest challenges were the timelines, and getting all parties coordinated; this resulted in the initial procedures being quite lengthy, time-wise, allowing a lot of time for coordination of the process. As we have gained experience and built up the interactions with HTA body colleagues, the parallel process now includes shorter timelines and more flexibility. The EMA has received quite a few comments on the draft guideline during the consultation process, and many of these are asking for more clarity on responsibilities

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during the procedure. However, refining a joint process (EMA and HTAs) is potentially more complicated than, say, with an EMA-only procedure. Nevertheless, there has been lots of engagement and positive interaction during the procedure development with HTA colleagues.

In addition, in the pilot procedures, especially where divergent opinions exist, the EMA and HTA bodies have worked together to try and find a way forward. The pre-face-to-face teleconference really helps to work through these issues and provides time for the applicant to digest the issues and prepare for the face-to-face meeting. The longer lead-in compared to standard scientific advice may mean that applicants need to plan more in advance. We also recognise that SMEs [small and medium-sized enterprises] are concerned about resources needed and complexity of the HTA environment when thinking about participating in parallel EMA–HTA scientific advice. We also think that payers are another stakeholder group that needs to be further engaged.

Q: **Acknowledging the draft Best Practice guideline for pilot EMA–HTA parallel scientific advice procedures, were alternative procedures to the SAWP advice procedure considered? Have any comments been received from HTAs on the proposed process?**

A: The new process had to dovetail into what was already in place for scientific advice but be adapted to meet the needs for HTA bodies. A lead-in of four to six months (as per the draft guideline) helped the coordination and helped the HTAs to schedule sufficient resource; they need a minimum of three months with the dossier in order to participate in the face-to-face meeting. Yes, definitely participating HTA bodies are involved in any decisions on this multi-stakeholder procedure.

Q: **A briefing document outline has been suggested by both the EMA and the HAS [Haute Autorité de Santé] SEED Consortium for advice procedures; would you consider using the same document template?**

A: The EMA's template is just a guide, not a strict expectation (a package in another format would still pass validation). The EMA has reviewed the content in its draft template against the SEED template and they're roughly the same. I can see alignment of the templates in the future, once the SEED pilots have been completed and we have more experience. The objective for both initiatives, which work in close cooperation, is to test and implement the best possible model, including templates. In summary, we are flexible in the structure of the document.

Q: **Can you comment on how parallel scientific advice at a national level is perceived by the national competent authorities [NCAs] and HTAs, given that differences in uptake of parallel advice procedures still exist?**

A: Of course, I can't speak for the NCAs, but evidence shows that NCA regulators feed into the existing SAWP process and they have always been willing to participate in parallel advice procedures – I have never had an NCA refuse to participate. We do see that there is a tendency for a core set of HTAs to be requested to participate in parallel advice; there are some HTAs – such as Norway, and some bodies in Spain – that are willing to participate but they don't seem to be approached by companies.

The SEED pilots are also ongoing, and the EMA will participate in three of the seven procedures planned for medicines. The first of these was completed in October 2014 and involved 12 HTAs. The uptake of parallel advice is promising – by the end of 2014 there will be a total of 35 ongoing or completed procedures (two of these via the SEED pilot). Mostly they involve large companies, but SMEs can still benefit from the added value of knowing what could be (and what wouldn't be) acceptable from a HTA perspective, but perhaps we need to look more at providing help to small companies in this regard.

Q: **The EMA roadmap to 2015 indicates that the EMA will collaborate more closely with HTAs. Can you comment on whether the due objectives of the 2015 roadmap have been met to date (eg, post-licensing data generation), and what the challenges are/were?**

A: Well, in terms of the general guideline exchange, the EMA has commented on the draft EUnetHTA guidelines and vice versa (at the public consultation stage). The first EUnetHTA therapeutic guidance (for osteoarthritis) is in the elaboration phase but the framework is there for enabling input. The EUnetHTA meeting minutes from July provide an overview of the information exchange, and this will also be on the agenda for further discussion at the EMA–EUnetHTA meeting in December.

The Post-Authorisation Efficacy Study (PAES) scientific guidance is in development; we have to remember that these studies are not a route to early approval. We can explore how HTAs can be involved in the planning for such studies, through the scientific advice process when PAES are discussed. Similarly, we emphasise the need for drug developers to proactively plan data collections including those post authorisation, even PASS [Post-authorisation safety studies], or PAES, may be considered, and engaging with scientific advice in the process. We are interested in how registry data collection can be better planned. We are developing the PRAC–SAWP interaction to further support additional input into the process.

Q: **With the increasing collaboration between the EMA and HTA bodies, is there potential for overlap in assessments? Does this offer any learning opportunities, and can you foresee the CHMP [Committee for Medicinal Products for Human Use] placing more emphasis on HTA-relevant criteria in the future?**

A: Well, I see the common scientific methodology of critical appraisal used by HTAs and regulators when looking at clinical trials reassuring, and of course overlap can enrich the debate. However, it is absolutely

critical that each party sticks to its remit. For instance, regulators will not "gold-plate" advice (in that they will not look to add on/pre-empt HTA body requirements). Having these parties sitting down in the room together with the applicant and 7 other stakeholders, and listening to each other's views, provides the platform to rationalise the evidence collection; this is the core of a parallel advice discussion. Population, comparators and endpoints are often areas of greatest debate. We must remember that active comparators do have a role to play, and they are often needed for benefit–risk assessment by regulators.

***Q:* What do you see as the biggest challenges facing EMA–HTA parallel advice discussions in the next five years, and how could these be overcome?**

A: I see that there are a number of challenges and goals, both short- and long-term. Initially, we need to optimise the procedure (which will involve addressing comments from the guideline's consultation on ownership of the process across the EMA and HTAs, and defined roles), and the first working group teleconference has already taken place. Then, we will need to take on board lessons from the SEED pilots and refine the process for the medium term when we have more experience. I'd also like to see a scientific group to look at methodologies (eg, population issues, endpoints, duration of follow up, standards of data collection and analysis) in terms of where efficiencies in evidence generation can be garnered and be acceptable to both regulators and HTA bodies.

In terms of policy, the Commission has already highlighted the importance of fostering cooperation between HTA bodies. The recently established HTA Network (Article 15 of Directive 2011/24) has just adopted its strategy, in which the importance of working more closely together and with regulators is well-outlined. We need to see how the HTA bodies will take those suggestions forward. We also need to move towards a "lifecycle approach", and start to see parallel advice as something that can occur throughout the process (eg, the discussions around adaptive licensing clearly indicate the need to bring HTA bodies on board early in the development process so they are aware of the planned strategy) through to the post-authorisation phase. Finally – and this really is a long-term goal – I would like to be able to show the value of parallel advice on market access, similar to what has already been shown for standard scientific advice (increased chance of success at the time of marketing authorisation).

***Q:* Finally, on a more personal note, what book are you currently reading?**

A: I'm reading *The Goldfinch* by Donna Tartt. I love seeing goldfinches in my garden, so this was quite a personal gift. It's extremely evocative and highly descriptive, but I like the detail and am enjoying it. I've just reached the "first crisis" point in it but it is work in progress and I will see how it evolves.