It is well known that both the European Medicines Agency (EMA) and EU member state national agencies will offer scientific advice (SA) to drug sponsors at any stage of the development process. This advice can be extremely helpful to sponsors in designing trials and choosing end points. Following the advice on these matters mitigates the risk that regulators will later object to them when they assess the corresponding market authorization applications (MAAs). The advice provided by either the EMA’s Committee for Medicinal Products for Human Use (CHMP) Scientific Advice Working Party (SAWP), or one of the European National Competent Authorities (NCAs) is not binding, but it can certainly be useful.
Indeed, the importance of adhering to SA was highlighted by a 2015 article in *Nature Reviews Drug Discovery* which noted that between 2008 and 2012 85% of applications that received and followed early scientific advice ultimately received marketing authorization (MA), as opposed to only 41% that did not.1

However, while the advantages of seeking and adhering to the advice given by the EMA are clear, there are also several possible drawbacks. It is critical, therefore, for sponsors to know when during their clinical development program to seek regulatory SA, and whether to request this from the EMA or NCAs. The choice depends in part upon the MA route the sponsor is planning: centralized, through EMA or National, mutual recognition, or decentralized.

**CENTRALIZED VS. OTHER MA PROCEDURES IN THE EU**

For many medicines, such as monoclonal antibodies and all orphan drugs; and for certain therapeutic areas, such as oncology; MA must be pursued via a centralized application to the EMA. However, for other products and indications where the centralized route is not mandatory, sponsors can opt for a national MAA.

In the case of a centralized procedure, the sponsor may wish to have informal SA with an NCA in advance of an EMA SA procedure. In that case the NCA is best chosen on the basis of its recognized experience; if for example the targeted therapeutic area is diabetes, it would be best to pick an NCA noted for that indication.

Requesting SA from a national agency rather than CHMP can be a faster, less expensive process, often with the opportunity for face to face discussion. In contrast, submission and review timelines for SAWP meetings can take up to four months (if a pre-submission meeting is planned and if the SAWP requests a face-to-face meeting with the sponsor), and never less than two. National agency timelines vary, but in general are shorter — sometimes as little as four weeks. National SA also is delivered in a less formal, face-to-face format, as opposed to CHMP’s SA, which is a written procedure [unless the SAWP requests a meeting to address issues that have raised concerns].

On the whole, requesting SA from national agencies can be a less daunting proposition than from CHMP.

That said, minutes from national SA, just like CHMP SA, must be included in MAA, whether the sponsor is pursuing a centralized or decentralized approach. If the sponsor, for whatever reasons — for example, developments in scientific knowledge, or outcomes of clinical trials in other studies — elects not to follow the SA, that must be explained.

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In PAREXEL’s experience, there are several benefits of obtaining SA, and some hazards to avoid.

**SA Benefits**

- Can strengthen the value argument through the process of preparing the briefing documents and clear questions for the regulators
- Can clarify overall CMC non-clinical and clinical issues in agreement with regulatory authorities
- Can establish early agreement on the design of clinical trials
- Can avoid regulatory delays by refining trial design and defining end points that are acceptable to regulators
- Helps the sponsor establish a working relationship with regulators
- Improves the chances of favorable outcomes if the advice given is adhered to

**SA Hazards**

- A poorly-prepared briefing document will increase the chance of an unwanted outcome.
- A failure to achieve agreement on the proposed development can lead to delays and increases in costs.
- For novel therapies or new therapeutic approaches with no existing guidelines, insufficient background information will lead to a more challenging process.
- Obtaining and observing regulatory SA does not guarantee that HTAs will accept the end points; it also makes sense to obtain early HTA input or to consider joint regulatory and HTA SA meetings.

convincingly, with data and justification to explain the deviations from the SA, as well as the sponsor’s course of action.

Sponsors can seek advice from both CHMP and national agencies – they are not mutually exclusive. But developers must consider their resources and project horizons in seeking SA as part of their overall regulatory and commercial strategies. A developer planning a centralized MAA should seek SA from the EMA, in order to have agreement from CHMP in advance of the phase III trials.

Most importantly, whatever authority is approached for advice, sponsors must prepare well for the meetings.

They must carefully consider the issues on which they would like advice, reflect on the consequences of possible responses, and judiciously draft the company position on each issue raised.

In PAREXEL’s experience, the positives of seeking SA generally outweigh the negatives. But sponsors need to know what will be required, and the importance of timing, the choice[s] of regulatory bodies, and of high quality briefing documents.

In other words, SA will help those who help themselves.
WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.

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