



Seeking Parallel Consultation

The rationales and results of engaging early with regulators and HTA bodies.

Engaging early with regulators and Health Technology Assessment (HTA) bodies gives the opportunity to get input on key aspects of drug development. This is however far from the only reason companies have for seeking advice before starting their pivotal clinical trials.



At NDA we've worked with hundreds of companies over the years, provisioning specific scientific advice ourselves, or preparing development teams for critical interactions with the agencies. Over this time, we've seen a diverse range of reasons for embarking on this process. In this white paper we will look more closely at some of these reasons, provide a short overview on the current state of the system and elaborate on what the expected outcomes of constructively engaging with regulators and HTA bodies could be.

The many routes to scientific advice

In Europe there are many routes to gain scientific advice directly from official authorities. National regulatory advice is a routine practice of most regulatory agencies, as well as of the European Medicines Agency (EMA).

Scientific advice in the HTA arena is more recent. In this context, national HTA advice is provided against the backdrop of country or region-specific policies and legal requirements. Early dialogue involving multiple HTA bodies is also rather recent, provisioned in the context of the European Network of Health Technology Assessment (EUnetHTA) Joint Action 2 as well as specific actions financed by the European Commission (SEED) and involving both EMA and EUnetHTA.

Indeed, in recent years, EMA and EUnetHTA have led several combined regulatory-HTA pilots to get experience both on the process and the content of such an exercise ^(1,2,3).

Since the creation of our NDA Joint Advice service offering in 2011, the NDA Advisory Board has also conducted numerous such projects for clients, focusing on ensuring a thorough understanding of the varying regulatory and HTA requirements and bridging the relative efficacy – relative effectiveness gap.

The means to gain scientific advice are many and diverse, but so are the reasons companies strive to get it.

Why seek scientific advice?

The combined scientific advice/early dialogue processes allow a company to engage relatively early in discussions with regulators and HTA bodies. The label on the tin indicates that the main interest of such an engagement would be *to gain scientific input into the development program of a product to be able to steer it away from regulator, HTA and payer pitfalls and towards rapid patient access.*

The scientific input usually covers the proposed study design(s), comparators, endpoints, target study population and inclusion criteria's, study length and other key aspects important both for regulatory and HTA bodies. More in general, this early discussion will allow a company to check if the evidence to be generated for EMA is relevant for HTA submissions.

Asking for a combined regulatory and HTA advice is even more important in cases where treatment guidelines are weak or inexistent and/or there is no relevant HTA decision available in the field of interest.

Reality, however, is even more diverse than this and the reasons and rationales for companies to go for scientific advice therefore vary greatly.

Stake holder engagement

Engaging early with regulators and HTA bodies can be a crucial motivation for engaging in the scientific advice process, as it provides a unique opportunity to introduce these two key stake holders to the science and circumstances behind the company's product. This can benefit the process in two ways:

1. In any future engagements the regulators and HTA bodies will know the product/technology and targeted patient population better. This will potentially enhance future interactions and remove communication hurdles.
2. By engaging with the right individuals in the right agencies, interest in the product can be sparked which can lead to constructive and positive input along the product's development path. Building rapport with assessors are again an important vehicle to frictionless communication.

Demonstrating progress

Engaging with external experts in a structured manner is also an excellent way to demonstrate to boards and stake holders that the product is progressing through the development process. Constructive feedback from regulators and HTA bodies can help steer the product development but can also be a value driver for the company.

If this is a main driver for expert engagement or seeking scientific advice, other reasons should also be carefully considered to optimize the value of the interaction. Seeking endorsement for the sake of it is rarely the optimal use of the time spent by external experts or regulatory agencies and HTA bodies.

Compliance

Many multi-product pipeline companies have highly controlled processes for how to progress products through the development process. This may well include the consideration and execution of a formal scientific advice procedure.

As this reason is not a value driver in itself, the reasons that the company put this requirement in place in the first instance should be carefully considered when running through the motions. Teams following a check list risk missing the underlying strategic reasons for why the process is necessary and may therefore not consider alternatives or options that might fit better or add more value.

Internal alignment

Although not its primary purpose, internal alignment is an incredibly valuable potential outcome of any scientific advice/early dialogue process. Teams working towards a clear goal along a clear timeline tend to glue together and more easily visualize the ultimate outcome. At NDA Group we've seen many occasions where the formal process has created strong composite teams.

These teams are primed to progress the product through development with a determination and shared purpose that would not have been possible without the structure and clear goal that the scientific advice process offers.

Achieving internal alignment should therefore always be considered a potential beneficial outcome and should be planned for accordingly.

The state of the system

Once the fundamental rationale behind seeking scientific advice is well understood, understanding the current state of the system is the next step.

As described, there are numerous ways to achieve national scientific advice from both a regulatory and a HTA standpoint. If the purpose is to gain insights from regulators and HTA bodies in parallel, the options have however evolved significantly in recent years. Some of the important changes have been introduced as recent as in 2017. The experience of combined consultations with the EMA and EUnetHTA has led to the establishment of a new platform on evidence generation based on Parallel Consultation (PC) ⁽⁴⁾, replacing the previous Parallel EMA-HTA Scientific Advice procedure, EUnetHTA's early dialogues and the SEED (Shaping European Early Dialogues) project.

The purpose of the new procedure remains the same but introduces some changes:

- A stable group of HTA bodies with significant experience of conducting early dialogues has been assembled to improve consistency, quality and learning throughout the process (Early Dialogues Working Party – EDWP).
- A coordinator and rapporteur for early dialogues is appointed to increase the proportion and quality of common answers.
- The scope for early dialogues has been extended to cover Post Launch Evidence Generation (PLEG).
- Finally, an EUnetHTA early dialogue secretariat has been established to improve logistics and project management.

In addition to these changes it is now possible to make one single request for a Parallel Consultation, and through the whole lifecycle of the product, e.g. either before the start of a pivotal trial or regarding post-approval evidence generation. This is a significant improvement over the old procedure where the company had to contact the HTA bodies individually to check their availability.

The number of Parallel Consultation slots remain limited – a significant challenge with the existing system. This means that the process is currently only available to products expected to bring added benefit to patients by, for example, a new mode of action, and that are targeting life-threatening or chronically debilitating disease, and that are responding to an unmet need.

For all products outside of these criteria the option is to turn to other forms of scientific advice and other sources of external expert advice, such as the NDA Advisory Board's Joint Advice process.

The process

Parallel Consultations (PC) start with the submission of a letter of intent followed by a Briefing Book sent to EMA and EUnetHTA's Early Dialogue Secretariat. The Briefing Book follows a standard format and should include the questions that the sponsor wishes to discuss.

During the face-to-face meeting, the EMA and HTA bodies will discuss and provide answers to the questions raised by the sponsor. This will be followed by written reports from the EMA as well as EUnetHTA.

PC may be organised either as consolidated PC or individual PC ^(Figure 2). Consolidated PC includes the full participation of the EDWP and up to 3 additional HTA bodies; in individual PC, HTA bodies participate based on their own national priorities.

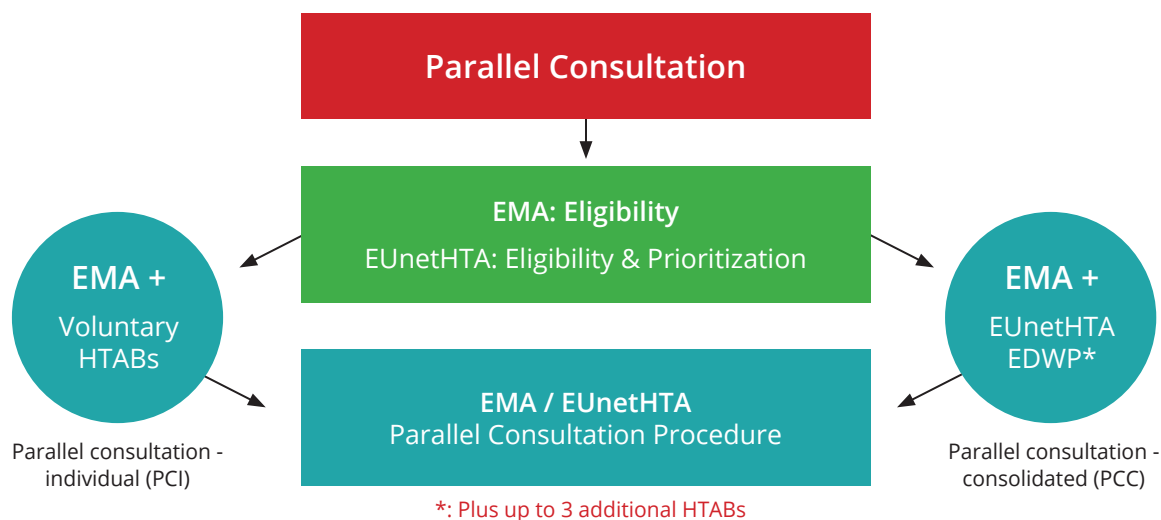


figure 2.

Careful preparation for this opportunity to engage with the regulators and the HTA bodies is critical – the topics for discussion will be those raised by the sponsor in the Briefing Book and nothing else, and the written reports continue to exist long after the meeting.

At NDA we've been working for 20 years to prepare a large number of teams for high-stakes interactions, such as the new Parallel Consultations, and have seen the difference it makes to approach these meetings 100% prepared. Ensuring high quality of the briefing material, optimising questions and securing beneficial written reports from the meeting and interpreting the Agencies' feedback in an unbiased manner, are all part of optimizing the outcomes of the consultation process.

Results of the parallel advice process

As parallel advice is still a relatively recent feature of the drug development landscape, little has been written on how it affects both the likelihood and speed to market access.

In 2016 a working group between EMA and some HTA bodies that participated in EMA- coordinated parallel EMA-HTA advices, published several important findings analyzing 31 recent procedures⁽⁵⁾. The focus was the degree of alignment that could be observed between regulators and HTA bodies regarding key aspects of clinical programs. The highest agreement observed between EMA and HTA bodies was around study population and the most significant disagreement concerned the choice of comparator. Regarding comparisons among HTA bodies, there was a high level of agreement for all domains of clinical development.

Importantly, in terms of evidence requirements, it was concluded that there was a high degree of overall agreement reached during the process, speaking strongly in favor of sponsors enrolling for parallel advice.

In 2018, Tafuri et al investigated the extent to which sponsors had implemented the advice provided by EMA and HTA bodies in updates to their clinical program (6). Interestingly, it was concluded that advice on primary endpoint had been considered in all cases, whereas advice on the choice of comparator was only accounted for in 60% of the cases. This is a clear indication of the challenges the sponsor faces in developing comparative data for different comparators. Differences in active comparators required by some HTA bodies necessarily introduce risks to technical success, and thus give reason to the sponsor to diverge from the HTA advice given, while following the regulatory advice in most cases.

The NDA approach

At NDA Group we have developed different options to optimize the provision of parallel scientific advice. The purpose of these different options is to take the key rationale of the sponsor into account to ensure that optimal outcomes from the process can be secured.

The NDA Advisory Board is a unique group of regulatory and HTA experts. Most of the Board's distinguished members led key activities related to the provision of scientific advice at the EMA, in national HTA bodies and in EUnetHTA.

NDA Joint Advice is one way to gain strategic advice and scientific input into the development program from a regulator and HTA body perspective without going the formal route, using the NDA Advisory Board instead. In particular, the NDA Advisory Board offers advice to sponsors on how to effectively bridge the relative efficacy – relative effectiveness gap and generate data adequate for both regulatory and HTA purposes. This is beneficial if time is of the essence and formal advice timelines don't fit into the sponsor's schedule, and when the sponsor is looking for input in a safe harbor environment. Experience has shown that it is very challenging to run formal parallel consultation in a timely manner between phase 2 readout and initiation of phase 3 studies. In this scenario NDA's Joint Advice is an ideal proxy to the Parallel Consultation process.

Preparation for scientific advice or Parallel Consultation is another service NDA Group deploys to optimize the value sponsors can achieve from engaging in the formal process. When Agency engagement is a key driver of the process, NDA ensures that questions are optimized and support the sponsor with writing or optimizing the briefing material. Strategic input on the most relevant route for scientific advice is also a common part of this process.

Through these highly flexible and tailorable service options NDA Group can ensure that every sponsor can reduce the risks in their pivotal program, regardless of technology, therapeutic area or timeline.

References:

1. Best Practice guidance for Pilot EMA HTA Parallel Scientific Advice procedures. For consultation. EMA/109608/2014
2. Report of the pilot on parallel regulatory-health technology assessment scientific advice. EMA/695874/2015
3. JL Harousseau, M Pavlovic, H Mouas, F Meyer. Shaping European Early Dialogues: The SEED Project. Value in Health 2015 (18), Issue 7, page A562
4. Guidance for Parallel Consultation. EMA/410962/2017
5. Br J Clin Pharmacol. 2016 Oct;82(4):965-73 Tafuri G, Pagnini M, Mosley J et al. How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice
6. Br J Clin Pharmacol. 2018 Jan; Tafuri G, Lucas I, Estevao S et al. The impact of parallel regulatory-health technology assessment scientific advice on clinical development. Assessing the uptake of regulatory and health technology assessment recommendations