



Maximizing the Value of Early Engagement Between Manufacturers, Payers and Regulators in Europe – Key Lessons Learned From TCA’s Experience

By Nicolas Touchot

During the recent ISPOR meeting in Dublin, a plenary session was dedicated to “Early Engagement Between Manufacturers, Health Technology Assessors and Regulators”. This session described the parallel scientific advice process involving the European Medical Agency (EMA) and several European Health Technology Assessment (HTA) Bodies as well as the NICE-MHRA advice in the UK, and the EUnetHTA involving multi HTA early dialogue.

These processes are all designed to help companies develop products more efficiently and to improve the quality and the appropriateness of the supporting evidence. They involve a set of questions for regulators and payers, along with a company position for each question. These questions and company positions are relevant for the development plan and pertain to:

- Endpoints (primary and secondary)
- Comparators (clinical and pricing)
- Target populations, study designs and duration of follow-up
- Definition and demonstration of patient relevant benefits

Despite a limited experience, these processes have shown the potential for positive outcomes. During her presentation at ISPOR, Dr. Killalea from EMA described a case example where the company proposed a study vs. a placebo and vs. an unlicensed comparator. However, a study powered to show non-inferiority to the current standard therapy was not feasible due to the rarity of the indication. Ultimately a statistically less stringent approach was agreed, allowing the comparison to SOC and meeting all stakeholder requirements.

There is now almost five years of experience of early engagement, both bilateral between manufacturers and HTA Assessors and trilateral involving manufacturers jointly with HTA assessors and regulators. During the ISPOR session, a number of Key Success factors were consistently identified by the speakers.

Early Engagement Between Manufacturers, HTAs and Regulators Key Success Factors

Limit the number of questions to allow time to explore each question in details

Develop a precise but comprehensive value proposition to react to

Have company Regulatory and Market Access collaborate throughout the process

Approach meeting(s) in an open manner: be prepared to adapt, not just defend



We believe that early engagements between manufacturers, payers/HTAs and Regulators are extremely powerful tools whose use is bound to increase significantly over the years to come. However, these processes are time and resource consuming for all parties. For example, for the European parallel scientific advice, the review procedure itself is only 10 to 70 days, but preparation can last up to 6 months and requires input from many internal stakeholders.

In this ViewPoint, we draw from our experience in assisting two companies preparing for the parallel scientific advice process to develop our recommendations on how to maximize the value of early engagement between manufacturers, payers/HTAs and regulators.

Optimizing the Outcome and Value of Early Engagement



Educate all internal stakeholders on the objectives of the early engagement process and its measure of success

The objective of initiating early engagement with payers and regulators is to reduce the overall go-to-market risk. This overall risk can be schematically simplified as:

Overall Risk = Development Risk * Regulatory Risk * Market Access Risk.

It is necessary that all stakeholders clearly understand, and adhere to that objective. In our experience there is a natural tendency for each internal stakeholder group to want the advice to validate their own beliefs and positions. However approaching the process in this way is wrong. Early engagement is about defining and producing satisfactory arbitrages. Answers may mean more hurdles or investments for one internal team, but may facilitate the task or increase the chance of success for another team. For example a slight increase in development risk can be beneficial, if it comes at a low cost and reduces Market Access risk significantly. The development team must then be willing to support this outcome.

In our experience we even faced situations where certain internal stakeholders did not agree with the company's position on a specific question. The challenge is then to get these stakeholders to support a position that can be detrimental to their interests. This will only happen if all participants are fully educated about the process, about what to expect in terms of outcomes and about how the answers will affect their decisions moving forward. All must adhere to the fact that early engagement can only increase the overall chances of marketing the product at the desired price and for the broadest possible target population, therefore maximizing revenues.

Our practice suggests that most of the resistance comes from a lack of understanding. Some participants believe that engaging in early access is a way for senior management to check if they are right or wrong. Others fear that early engagement is binding and that if they have to "blindly" follow



the answers, thereby limiting their future decision power. Others believe that payers and regulators use early engagement to further increase the complexity of evidence generation. None of that is true but these concerns need to be alleviated upfront by clearly explaining a process that is often novel and slightly out of the “comfort zone” of most participants.

Nominate an unbiased “facilitator” to build consensus on questions and company position



Former British Prime Minister Margaret Thatcher once said: “To me, consensus seems to be the process of abandoning all beliefs, principles, values and policies. So it is something in which no one believes and to which no one objects”. Unfortunately internal stakeholders involved in early engagement sometimes feel that they have to abandon some of their beliefs and principles to develop consensus on the company position or even the wording of the questions. But contrarily to Margaret Thatcher’s rather cynical perspective, we feel that all participants should believe in that consensus, even if they did object strongly while it was developed.

Preparing for early engagement between manufacturers, HTAs and regulators requires a dialogue between teams that often do not communicate extensively internally, often speak different “linguos” and may have different personal and even financial incentives. To be successful, it should be totally dispassionate, taking the emotions and personal interests out of the process. Successful early engagements are those where ownership does not belong to one person but to the full team. Getting internal stakeholders to overcome their own desires and incentives is an important value outcome of the process, if not the most important.

As a result we believe that the person in charge of building the internal consensus should not be the leader of one of the key internal team vested in the outcome: regulatory, development or market access. Having been part of the various internal teams in the past is obviously a plus, but such individuals are rare. The brand manager could be a good facilitator, as he clearly has an incentive to maximize revenues but most companies have not allocated a brand manager yet at that stage of development. In our experience the best facilitator is not defined by his function or title, but rather by his experience to work across functions and his track record of achieving consensus.

External help can also be very useful in preparing for early advice. External consultants should be advisors and facilitators at the same time, providing process and possibly content expertise, as well as obtaining compromises toward a common benefit. The selection of external consultants responds to the same criteria than for internal facilitators: breadth of experience covering all internal and external stakeholders and ability to communicate with the various teams. External advisors must not appear to be aligned with one particular stakeholder. For example “pure” Market Access consultants



will be perceived by regulatory and research to be biased. They are best brought in by the commercial team or by senior management.



Only ask questions for which answers clearly impact decisions

This seems quite obvious but in our experience, when we collected initial suggestions for questions from the different internal stakeholders, many of these initial questions were asked by teams mostly to get a validation of their opinion. The early advice process is simply too time and resource consuming for that.

Payers and regulators involved in the early engagement process will echo this opinion. They are quick to recognize questions for which the answer is unlikely to impact on the evidence generation strategy. To avoid answering “meaningless questions”, they have limited the number of questions that the company may ask. Despite that fact, they are still often faced with questions of low impact value. One payer involved in several early engagements commented that companies often start by asking generic questions such as “do you agree that there is a significant unmet need for novel products in the targeted indication?” Then, smiling, he added “And if we say no, do you really believe that the company will stop the development of the product....?”

So for each question, we suggest to anticipate the impact of the outcome:

- What is the implication of agreement or disagreement by the review committee? This implication must be a clear change in the development plan or in the value proposition.
- If the answer does not change the development plan, the TPP, or the product positioning, our belief is that it should simply not be asked.

Prepare the questions and the company position through pre-work with regulators and payers



One can ask why is it necessary to go informally to payers before going formally to payers? We believe that this is crucial. The more precise the questions, and the more precise the corresponding company positions, the more useful the answers. In our experience, doing a limited number of payer interviews (8-10) prior to putting together a dossier for early engagement allows significant refinement of the content and the wording of the briefing package. This is a small incremental investment to the overall process with high return.



While asking questions, it is important to understand which data needs to be provided to allow regulatory and HTA participants to develop educated answers. It is also important to understand what will drive these answers, in order to make sure that all the information is provided in the documentation supporting the company position. Finally it is important to understand how to best phrase the questions so they fit within the payers' mindset and analysis process.

Pre-work with payers may also allow reducing the number of questions. If a question appears to relate to a non-issue during preparatory payer interaction, it can be eliminated, thereby freeing time to focus on high impact questions. For example, in one of our project, the company initially wanted to ask a question on the acceptability of Asian patients in a pivotal trial for a rare disease. During preparatory interviews, payers asked if there was a genetic or another ethnic component to the disease. Since no data suggested that Asian patients may react differently to patients from other ethnicities, they considered that the presence of Asian patients in the pivotal trial was not a concern for them and suggested to take that question off the final briefing package.

Be willing to show flexibility during review meetings, but within pre-defined limits



The success of early engagement between manufacturers, HTAs and regulators is measured if the outcome is a position that is agreed by all stakeholders while still meeting the objectives and the constraints of the company. This is different than trying to convince payers and regulators that the company position for each question is right. So it is important to enter the process with a certain level of flexibility.

In the early engagement process, regulators are willing to move away from standard regulatory study designs in order to demonstrate the patient benefits according to payer wishes, and payers are willing to accept and understand the constraints imposed by the regulatory process. In return, the company needs to be prepared to change its study design on the basis of the responses to its questions and on the discussions with payers and regulators.

On the other hand, there is no point exploring options if these are not possible. It is important to decide prior to developing the "briefing package" (ideally,) or prior to the review meetings (at least) what are the elements where the company position can be flexible and those where it cannot be.

For example if the joint advice committee asks (or is likely to ask) for a different comparator, but that comparator is not possible due to clear clinical reasons, we would suggest to:

- Explain this clearly in the briefing package to pre-empt any possible discussion

OR



- Address it as a question, as it will likely have come out as a topic of during pre-work discussions with payers

In either case, if it a discussion on that topic is likely to happen, walk into the meeting with a clear, rationalized and consensual position that this comparator cannot be used.

Additional TCA Recommendations

Consider completing the “Briefing Package” even if you do not intent to complete the overall process
The external and internal preparation still create significant value



While early engagement is certainly useful to obtain answers to specific questions, the process may become more time consuming or may simply not be possible for all products due to limited availability of payers and regulators. Some payers may be more incentivized than others, especially those who are developing a commercial consulting business around early interaction such as NICE, but the NICE model is unlikely to be repeated broadly and it provides only a single-country answer.

In our opinion, even if the process is not completed, there is a huge value to conduct the preparation externally and internally and to develop an “as-if briefing package”, thereby building the internal consensus around the company position. If the preparation work is done correctly and honestly (without bias, or need to validate the position of a particular stakeholder), the answer to most questions should actually be in line with the proposed company position.

Initiating an early internal dialogue between R&D, Market Access and Brand management is invaluable. This is often difficult to achieve and preparing for the briefing package provides the perfect framework for such interaction with a clear deliverable. Using this framework is a powerful tool to ensure that all key stakeholders in the company are aligned around a common set of beliefs and objectives during the development process.



Do not be afraid of this process even if you are a small company with limited resources
Dive In!

To date early engagement opportunities have mostly been used by big pharma. For example, out of the 25 first EMA European parallel scientific advice procedures, only 2 were from small and medium entities. While this shows that big pharma has clearly recognized the potential of early advice, it is



disappointing that SMEs shy away from it. We believe that SMEs would benefit most, as they usually lack the Market Access capabilities and resources that reside within big pharma. We have shown previously that SMEs often fail to include payer requirements in the design of their clinical trials (Touchot et al, In Vivo, June 11) and use of early engagement opportunities is a clear and obvious approach to correct this.

Many SMEs, especially non-European biotech companies have little awareness of the possibilities for early engagement with payers and regulators. Those who are aware often fear that they do not have the resources or the knowledge to complete the process. We believe that these reservations will contribute to broaden the gap between big pharma and small companies' ability to answer the needs of both payers and regulators. Unfortunately everybody loses in the end: SMEs if they go to market themselves and big pharma when they license-in products and need to make large "corrective" investments.

Conclusions

Early engagement between manufacturers, HTAs and regulators is a powerful approach that is likely to develop significantly over the next years. As every process that is based on answers given by one group of stakeholders to questions asked by another group, success hinges mostly on the quality of the preparatory work. This preparation needs to be both external to focus questions and help validate the company position, and internal to build consensus around that company position and to define flexibility and limits of that flexibility. But if done right and with the appropriate level of investment, it has the potential to significantly reduce overall risk in bringing products to market with a fair recognition of patient benefits and price / reimbursement status.

About Us: **Therapeutic Challenges Analysis** is an expertise-based management consulting firm dedicated to the business of healthcare. We are leaders in the analysis of the impact of Market Access requirements on clinical development, business development, and portfolio management decisions. **Nicolas Touchot** is a Managing Director at Therapeutic Challenges Analysis. You may contact him by e-mail at ntouchot@therachallenges.com.

About TCA ViewPoints: This white paper is part of a continuing series of TCA and Dr. Nicolas Touchot reports on the life science industry. For a complete list of our publications, please visit our website at www.therachallenges.com.

If you wish to learn more on how Therapeutic Challenges Analysis can help you prepare for early engagement between manufacturers, HTAs and regulators in Europe please do not hesitate to contact us.