executive insight
HEALTHCARE CONSULTANTS

The early bird catches the worm

Leveraging early payer engagement to shape your asset's optimal value proposition

The early bird catches the worm

Imagine the scenario. You spend years of scientific and commercial endeavour developing a genuine breakthrough therapy – a completely novel, first-of-its-kind treatment, offering hope to patients who had little before. The excitement builds towards submission, and finally, all the years of hard work and investment pay off with European-wide approval.

And then, nobody pays for it.

It's a nightmare scenario, and exactly what happened to biotech company UniQure with its gene therapy Glybera for a rare genetic disorder called lipoprotein lipase (LPL) deficiency.

It serves as a stark reminder that Health Authority / regulatory agency approval does not mean reimbursement and market access. And that thinking about payer considerations is just as important in the early stages of drug development as the clinical considerations. A treatment might be ground-breaking in the clinical setting, but if patients can't access it, what's the point?

What payers want

While it is true that the payer landscape is complex and fragmented across geographies, the need to see value for money – products resulting in measurable, beneficial outcomes (to patients and payers as well as HCPs) at prices that are sustainable for healthcare systems – is a priority for all.

At present, much early drug development is driven solely by demonstrating clinical value, with few other market dynamics such as affordability or value for money taken into consideration. But understanding the payers' definition of what constitutes value for your product is just as important – and this needs to be done early, so there's enough time to design clinical programs accordingly.

Before phase II

Seek payer input early on.

Glybera: a cautionary tale

In 2012, biotech company UniQure made history with the first ever EMA approval for a gene therapy. The regulatory green light for Glybera – for a rare genetic disorder called lipoprotein lipase (LPL) deficiency that causes a build-up of fatty deposits in the blood and several critical organs – was hailed by many as a decisive moment in gene therapy. But fast-forward five years to 2017 and with only a single patient treated, the company conceded defeat, selecting not to renew the therapy's license.

Glybera was formally evaluated through HTA in Germany and France, both of which rejected it. The eye-watering price (€1.1 million per patient) was certainly an issue, but there were others along the way. The drug was given to just 27 people in trials with no control arm and the tests never showed a lasting improvement in fat levels in the blood. In Germany, Glybera was initially positioned as a community product, then as a hospital-only product as the company tried to work out the best way to optimize reimbursement. These kinds of issues could have potentially been anticipated and addressed with earlier payer engagement.

But while companies are used to connecting with regulatory agencies at an early stage in the development lifecycle, relatively few take the plunge with payers or health technology assessment (HTA) agencies. This may be for various reasons, including a lack of knowledge about payer dialogue within organizations, a disconnect between R&D and Commercial within the company, the investment of time required or simply a degree of wariness of payers.

"Advanced preparation for market entry is really something the industry can do a lot better than it currently does," says Dr. Dan Ollendorf, Director, Value Measurement & Global Health Initiatives at the Center for the Evaluation of Value and Risk in Health, Tufts University School of Medicine (USA). *"Conversations really need to be had with payers before Phase 2 so that pivotal trials can be designed to help demonstrate the measures that matter most to reimbursement authorities, but often that just isn't happening."*

So, what options are available to the pharmaceutical industry for early payer dialogue?

The what, why and when of early dialogue with payers

Early dialogue between pharma and payers can take various forms (see Table 1).

Table 1: Types of Payer Engagement

	Informal guidance		Formal guidance		
Type of engagement	**Advisory boards**	**Telephone interviews / message testing**	**National HTA guidance**	**Supranational payer guidance**	**Parallel guidance with EMA**
Description	Advisory board with a group of key opinion leader payers.	One-on-one telephone interviews with payers.	Formal process offered by national HTAs e.g. NICE (UK), G-BA (Germany), TLV (Sweden), HAS (France), AIFA (Italy), CADTH (Canada)	A multi-HTA early dialogue approach by EUnetHTA, providing consensus across several EU national HTA bodies.	Coordinated by the EMA and EUnetHTA, this process allows companies to obtain feedback from regulators HTA bodies on their evidence-generation plans at the same time
Benefits	Relatively easy and inexpensive to organize.	Relatively easy and inexpensive to organize.	In-depth formal input at the country level.	In-depth formal input at the supranational level.	Simultaneous assessment of regulatory and reimbursement
Limitations	Limited set of KOLs may not be representative of actual HTA experience.	Individual opinions, which may not be representative of actual HTA experience.	Significant time investment, advice for only one country.	Significant time investment, advice may not be relevant for all countries.	Potential for contradictory guidance from multiple HTAs.

The most well established – and potentially the most valuable – format for early payer engagement is an official HTA advice service, either at the national or supranational level. Early HTA advice is often called scientific advice and is a process that enables manufacturers to collect non-binding feedback on clinical trial design, target populations, key outcome measures and other considerations, directly from payers at a pre-launch stage. It provides a fantastic opportunity for both stakeholders to align on clinical development programs and ensure appropriate access for patients.

"There are significant potential benefits for pharma companies," explains Ollendorf. *"Early scientific advice can provide crucial insights into HTA regulations, companies can benefit from specific clinical trial design feedback and they can even gain an early understanding of future HTA expectations."*

However, what it absolutely is not is any kind of guarantee of reimbursement. All HTA feedback is strictly non-binding.

It is also important to remember that early dialogue can be just as beneficial for HTAs. Assessing the value of new medications is often difficult, with innumerable variables involved. Once you start adding in unknowns – which is particularly the case with novel therapeutics and orphan drugs with no meaningful comparators available in the market – then it becomes particularly challenging. Early dialogue can help them to get a crucial early foothold in evaluating a therapy's value.

When should it happen? In general, prior to the design and initiation of the pivotal Phase 2/3 clinical trial to ensure the trial can be designed in the optimal way to demonstrate value to payers.

The process can take up to 6-8 months to complete due to the need for internal alignment and back and forth with the HTA body. But it is possible to reach out too early. If there's a lack of internal agreement on key decisions about, for example, major trial design

No guarantee

Early scientific advice is non-binding.

decisions (e.g. the target population), then early dialogue with payers will not solve that for you.

> **Why companies can't afford to ignore the value proposition in trial design**
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> GlaxoSmithKline's (GSK) Benlysta (belimumab) was the first therapy to be approved for the treatment of lupus in over 50 years. But despite Benlysta's first-in-class status and the high unmet medical need associated with lupus, payers couldn't see the value for money in the supplied evidence and came back with negative appraisals.
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> IQWiG in Germany concluded that Benlysta brought no added therapeutic benefit as GSK failed to provide the relevant data to assess the benefit of its medicine versus "optimized standard therapy". If GSK had sought early advice, this could have been fixed in the trial design.

National scientific advice: time-consuming but worth it

Early advice can take place at the national or supranational level. In Europe, at time of writing, the UK (NICE), Germany (G-BA), France (HAS), Italy (AIFA) and Sweden (TLV) offer some form of HTA advice service to the industry. Outside of Europe, CADTH in Canada & PBAC in Australia also offer early scientific advice and ICER in the US is considering such a program.

The benefit of gathering early advice via a national process is that manufacturers receive country-specific HTA recommendations, which may expedite the future process of seeking reimbursement at a local level.

The level of service and cost differs quite significantly between markets – for example, NICE in England offers the most customizable option but with relatively high fees (although reduced fees are possible for small and medium sized enterprises), whereas HAS in France has narrower options available, but advice is free.

Country-specific

Seeking clarity on national HTA level.

All will require some form of “briefing book” – a country-specific central repository of all the crucial information and questions that the HTAs need to see. This is the most important step in the process, and time should be invested to ensure the briefing book is as comprehensive as possible. You will have the opportunity to ask questions to the HTA – these should not be too open-ended, but rather seeking clarity on well-considered elements of your program. This early work will shape the value of the subsequent discussions, so it is important to focus time, energy and resource at this stage.

A subsequent face-to-face meeting offers the opportunity to get answers to some of those crucial questions. Key decision makers from the pharmaceutical company should be present at the meeting, including senior clinical leads – it offers them a vital opportunity to gain consensus with the clinical experts from the HTA panel.

It’s a time-consuming process but considering the potential pay-off years down the line, well worth it.

Combined approaches

Alternatively, there is the option for combined simultaneous EU payer guidance. EUnetHTA has piloted a Multi-HTA early dialogue approach to provide a cooperative/consensus advice across several EU national HTA bodies, and NICE and CADTH have also recently launched their own parallel program. The aim of Multi-HTA dialogue is to reach a consensus advice for the manufacturer, but there are obviously challenges in obtaining consensus advice from all payers in different countries.

Multi-HTA dialogue

Aiming for consensus advice.

Finally, there is the option to combine payer guidance with EMA regulatory guidance. Scientific advice is coordinated by the EMA in association with national HTA bodies to bring all stakeholders together to provide the manufacturer with early scientific advice. Several HTA agencies can be invited to participate in the process, but again the advice will likely differ across markets, which can bring its own challenges for companies.

“It’s a no brainer”

The NICE website includes a great case study from Takeda, who utilized NICE’s scientific advice during the design of a clinical trial for a key pipeline therapy.

Ross Selby, Head of Global Patient Access at Takeda Oncology talks about how the scientific advice plays an essential part of their strategy building.

"As a team, we decided to use the services to help overcome any uncertainty we had with the clinical trial design. For example, the different comparators, the end points and the impact on the clinical trial outcomes. The scientific advice team supported us in refining our value proposition and optimizing our trials, ready for the health technology appraisal (HTA). We made sure we engaged early enough so our clinical development teams could further optimize the trials after the advice was given.

"Once we received the scientific advice report, we were able to make changes to the secondary end points on our pivotal clinical trials. This helped NICE and other HTA bodies to assess our medicine further past the primary endpoint. The advice on our patient reported outcome measures and when to measure them has been particularly useful for our outcomes research teams.

"To summarize, I would say that the scientific advice services have been fantastic. There is a spirit of support amongst the team and this reinforces that NICE want to approve valuable medicines; they just need the appropriate evidence to do it. I would thoroughly recommend their services, for me it's a 'no brainer'.

Uncertainty is the prime reason that medicines struggle with health technology assessment. Scientific advice is a mechanism to reduce that challenge - so take it."

Reference: Naissant G, Maignen F, Kusel J, Presented at ISPOR Europe 2019; NICE website, early advice case studies https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/case-studies

Improved value demonstration

What kind of feedback will you receive? Well, it could be potential challenges with trial design, for example issues with the comparator or trial endpoints. Perhaps you have selected surrogate endpoints that are not well established, or trial endpoints that don't fit the value proposition. Such feedback would require further internal alignment and potentially new evidence generation or selection of new / additional endpoints.

There could also be potential issues with the proposed economic model, for example the absence of a plan for survival extrapolation, requiring further follow-up from your Phase 2 trials. Ideally, companies should have done enough early modeling to address these issues, but early HTA advice frequently brings up considerations that may not have been appreciated previously.

Whatever the advice received, the company will have an opportunity to fix any highlighted issues and ensure the major pivotal clinical trial is designed in the best possible way to help demonstrate value in a meaningful way to payers.

Now what?

Implement feedback to improve value demonstration.

Conclusions

Pharma companies are comfortable with early regulatory agency engagement – now it's time for the early development strategy to include payers as well. Early planning is imperative in value-focused healthcare and payers want more manufacturer involvement in evidence development to facilitate their decision-making. When early payer engagement succeeds, it provides manufacturers time to design clinical programs that are more likely to meet payer evaluation needs. This will result in therapies that are more cost effective and gain quicker market access, benefitting manufacturers, payers, and patients alike.

Top tips

- Seek advice early, prior to the design of your pivotal trial, when you can do something about implementing the guidance you receive
- Ensure complete internal alignment before you start in terms of objectives and advice you are seeking
- Invest significant time on the briefing book and the questions you are asking the HTA – the more you put in at this stage, the more you will get out
- Consider talking to external experts to aid your question development
- Ensure you have the right people in the HTA meeting and the right level of seniority – although the team should be cross-functional, the key people are the clinical leads
- Consider practicing Q&As with the global team
- Avoid getting bogged down on one topic in the meeting, it can waste your allotted time
- Manage expectations internally. Paying for early advice is absolutely no guarantee of approval. It is important that everyone is clear on this
- Spend time after the meeting drawing up a realistic plan for implementing the feedback

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