As regulators lower evidentiary requirements for marketing approval to speed the development and review of new drugs for unmet medical needs, payers are demanding more data for these drugs to justify price premiums. This divide has left drug developers in a difficult position as they try to satisfy both parties in their clinical and commercial evidence plans.

On one side, for severe diseases with unmet treatment need, regulators increasingly accept clinical trial packages that lack large Phase 3 comparative randomized controlled trial (RCT) data and use intermediate surrogate endpoints to demonstrate a positive benefit-risk profile.

On the other side, payers want to see that a new product delivers clinically meaningful benefits (i.e., improvement in quality-of-life and morbidity/mortality endpoints that are directly relevant to patients) in well-conducted Phase 3 trials versus a locally-relevant comparator, as well as in more diverse, real-world settings. And they want those benefits to be cost-effective, delivering value for money. Payers therefore are increasingly using (and demanding) real world evidence (RWE) to inform their decision-making.

Recognizing the difficulty sponsors face in meeting their requirements, regulators and payers have developed programs to help companies get early, formal advice and guidance on how to build an evidence generation plan that will provide the optimal data package for each.

However, developers who (wisely) seek early advice and engagement often find it challenging to reconcile input from stakeholders with differing mandates and goals (see Table 1). Meetings and discussions alone can’t align these differing needs, and there’s no such thing as a perfect evidence package because there are always tradeoffs between time, costs, risks, and utility.

Therefore, companies need to be strategic in how they engage with regulators and payers to navigate these complexities, and to avoid duplicating work and creating unnecessary challenges for themselves.

REGULATORY APPROVAL WITHOUT MARKET ACCESS IS A PYRRHIC VICTORY

The industry’s pipeline is increasingly dominated by transformational therapy classes: CAR-T cell treatments, immuno-oncology, and gene therapies. At the same time, the proliferation of accelerated regulatory pathways across the globe are offering streamlined, more flexible approaches to drug development. For example, if results warrant, it’s now possible for a first-in-human trial of an experimental oncology drug to morph, without pause, into a pivotal efficacy trial.

Developers must seek advice on the regulatory requirements for these technologically advanced products, and novel, possibly curative (i.e., single-use) treatments. But regulatory approval does not necessarily confer commercial viability.

For example, Glybera®, a gene therapy to treat a rare metabolic disease that triggers pancreatitis, was granted a five-year marketing authorization in the EU in 2012 under the category “exceptional circumstances.” But the manufacturer recently announced it will not renew the EU license when it expires in October 2017. Why? At a cost of $1.1 million per treatment, and addressing a condition
that affects only one in 1 million people (a total market of 150 to 200 people in the EU), Glybera® had only been used commercially and paid for once as of mid-2016. Payers decided that the evidence did not justify its price tag.

Payers and value watchdog organizations (especially in Europe) foresee further troubles for these novel drugs. In January 2017, the German health technology assessment (HTA) agency IQWiG (Institut fuer Qualitat und Wirtschaftlichkeit im Gesundheitswesen), ruled that the “additional benefit” of Xalkori (crizotinib) for non-small cell lung cancer patients with a ROS1 mutation was “not proven.” If this verdict is ratified, Xalkori would only qualify for reference pricing versus its generic chemotherapy comparators, rather than premium pricing.

In a press release announcing the verdict, Beate Wieseler, IQWiG’s Head of Drug Assessment observed, “The current dossier assessment... shows what problems can arise for early benefit assessments if drugs are approved early on the basis of relatively few data – we often see this, particularly in rarer diseases. If the European Medicines Agency (EMA) were to implement their ‘adaptive pathways’ plan and in future were to approve even more drugs with even fewer data, then this problem could be further aggravated.”

**EARLY ENGAGEMENT IS SMART, BUT YOU NEED TO BE SAVVY**

In the face of these ominous trends, the developer’s goal must be to create a tailored, data-based evidence plan that can reduce risk, guide rational development, support regulatory approval, and demonstrate product value to payers, prescribers, and patients in a timely (and affordable) manner.

Early engagement with regulators and payers is critical to such a plan, but it’s not always easy to obtain, interpret, or utilize such advice effectively. Here are five ways to get the most out of regulatory and payer guidance:

1. **Seek advice in the right places**

There are multiple mechanisms for formal, early interaction with both regulators and HTA bodies. The most advanced of these mechanisms exist in the EU and the United States. (See Table 2).

Data show regulatory advice can boost success rates and shorten clinical development time:

- An EMA study showed that between 2008 and 2012, 85% of marketing authorization applications (MAAs) that received and followed early scientific advice (SA) were approved, as opposed to only 41% that did not seek SA.

- Of 132 marketing applications submitted to the FDA between 2008 and 2012, the 49 which utilized a pre-Investigational New Drug (PIND) meeting had a median clinical development time (CDT) of 6.4 years; the 83 applications with no PIND meeting had a median CDT of 8.3 years.

For companies seeking advice on what payers want (which is what secures market access in many of the EU’s single-payer systems), Europe is the key arena for early engagement. But developers must tread carefully across the fragmented European HTA landscape, which encompasses 77 different agencies in 29 countries.

At PAREXEL, we advise clients to start engaging in countries with the most established early HTA processes: the UK, France, Germany, Sweden, or Norway. Select target HTA bodies based on factors such as standard of care (SOC)/treatment pathway for your disease, the track record of prior HTA results in your therapeutic area/indication, and the incidence rates of relevant conditions (which vary by country).

For example, Germany is Europe’s biggest market for pharmaceuticals, but it also has some of the most stringent clinical evidentiary requirements for proving “added benefit,” and for qualifying for potential price premiums. Recently, we advised a client to skip seeking advice [or reimbursement] from the G-BA [the main decision-making body of German physicians, dentists,
hospitals, and health insurance funds) because there were very few patients with the relevant condition in Germany (while there were many in both the UK and Portugal).

More is not better when pursuing early engagement with regulatory authorities and payers; identify the best, most relevant sources of advice, and pursue those.

2. Understand the risks

Early advice can help optimize pivotal clinical trial designs, and enhance data packages with relevant RWE, but it also comes with risks, including:

- The advice is non-binding. Regulators and payers can change their minds, and their advice, years later, when official product assessments are underway.

- Obtaining and adhering to advice is no guarantee that regulators or HTAs will consider the clinical data or RWE successful or sufficient once they examine it closely.

- Sponsors can only meet with a small fraction of the payers and regulators that will ultimately review their data dossier, so the advice they receive will, perforce, be incomplete.

- Early advice won’t protect against market changes 5-10 years down the road. For instance, if a blockbuster cure emerges that transforms an indication’s treatment pathway and a drug’s competitive landscape, all bets are off, regardless of the advice a sponsor has received.

Companies must perform due diligence and gather competitive intelligence to plan for many contingencies. Bringing suboptimal or poorly-prepared briefing documents to meetings could increase a sponsor’s chance of an unwanted outcome. If meetings end without agreement on the development plan, the result could be delays and increased costs.

These and other risks can be mitigated if companies pursue early engagement with a full understanding of the potential pitfalls, and address them proactively.

3. Do your homework

Many companies fail to appreciate that their role is not to be a passive recipient of information during meetings with authorities.

For example, too many companies wait for regulators to provide leadership and clarity on complex issues – like biomarker validation – instead of developing their own approaches. The FDA and EMA look to companies for leadership on novel technologies. And although regulators are properly cautious, they also are eager to break new ground, so long as the science is sound, and the studies well designed. Companies need to show up with data, plans, and a compelling rationale for both. Even if you think you have a good scientific backstory, it’s smart to introduce your ideas – backed by emerging data from your studies – as early as possible. Such an approach helps build mutual understanding with regulators.

Be an active participant in meetings. Summarize the discussion, outline agreements, and list action items. Make sure all concerns and questions have been addressed before you leave a meeting. Review the agency’s official meeting minutes (if they generate them), and notify regulators of any disconnects between your understanding and theirs. Ask for clarification.

Unless companies do their homework, they can’t push back (politely) when regulators or HTAs suggest including an additional analysis or endpoint that adds, say, three years to a clinical trial; you can’t talk about feasibility and utility unless you know your stuff thoroughly.

When it comes to nailing down what HTA agencies want from RWE, developers need to be well-prepared to get clarity on:

- Preferred comparator(s), patient-relevant outcomes of interest, whether surrogate endpoints will be considered, important patient sub-groups to analyze, and any other design issues with high levels of uncertainty.

- How to mitigate payers’ concerns about health economics modeling; that is, how to increase its credibility and reliability, making it more transparent and avoiding
debatable assumptions and accusations that the data are being cherry picked.

- How to prospectively identify (and then fill) gaps in evidence.

4. Right-size the advice you get

Regulators and HTA agencies will proffer advice, but they won’t make decisions for you. Companies must distinguish between nice-to-have and need-to-have advice and make judgment calls.

Payers have different perspectives. In Germany, for example, comparative clinical effectiveness is prized while cost-effectiveness rules in the UK. Therefore, companies should expect divergent advice, as well as concerns, warnings, and critiques; the key is to prioritize and leverage feedback to create better evidence plans.

5. Justify your decisions

Ultimately, sponsors are responsible for their development choices, including some that may not align with authorities’ advice. When that happens, companies will have to be prepared to defend their decisions in their marketing and reimbursement applications.

Sponsors can justify well-reasoned decisions that are both scientifically sound and pragmatic with respect to what is possible to achieve in the real world. In the EU, the minutes from scientific advice sessions with regulators must be included in any future MAA.

Documentation of all engagements is crucial, even if the agencies don’t provide a report. Sponsors need to substantiate advice given, and actions taken (or not taken). PAREXEL advises clients to create records of all meetings and ask for confirmation even when it’s not clear how much weight these documents will carry.

EARLY ADVICE CAN HELP INTEGRATE YOUR CLINICAL AND COMMERCIAL EVIDENCE PLAN

Integrating clinical and commercial evidence planning can create efficiencies and produce data that will promote both initial commercial success and sustained viability. But integration is no easy feat. For example, clinical teams may not want to wait for guidance from HTA agencies if they are intent on hitting development deadlines and if they fear that advice will be divergent anyway. That means commercial teams need to be at the table from the beginning to emphasize the risks of prioritizing a short-term development timeline over the longer-term prize of market access.

In the current complex environment of breakthrough medicines and treatments, and accelerated development pathways, companies with a strategic mindset that integrates clinical and commercial teams in early engagements with regulators and HTA agencies will benefit; companies that pass up the opportunity, or come to these meetings insufficiently prepared, will likely struggle to succeed.

Table 1. Divergent Mandates & Methods of Regulatory and Health Technology Assessment (HTA) Agencies/Payers

<table>
<thead>
<tr>
<th>Regulators</th>
<th>HTA Agencies/Payers</th>
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<tbody>
<tr>
<td><strong>Mandate(s)</strong></td>
<td>• Product Quality (i.e. Purity, Consistency)</td>
</tr>
<tr>
<td></td>
<td>• Safety</td>
</tr>
<tr>
<td></td>
<td>• Efficacy</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>Favorable risk-benefit ratio</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Perspective(s)</strong></td>
<td>Patients, Providers</td>
</tr>
<tr>
<td><strong>Evidence Types</strong> Preferred/Accepted</td>
<td>Randomized controlled trials (RCTs); For rare and/or severe diseases with high unmet needs: immature single-arm trial data with no comparative data</td>
</tr>
<tr>
<td><strong>Comparators</strong> Preferred/Accepted</td>
<td>Placebo; Usual or “traditional” standard of care (SOC); Historical controls</td>
</tr>
<tr>
<td><strong>Patient Population of Interest</strong></td>
<td>Tightly defined (homogenous in terms of disease) set of patients receiving meticulously documented, identical care in a controlled setting</td>
</tr>
<tr>
<td><strong>Endpoints Preferred/Accepted</strong></td>
<td>Clinical, including biomarkers/surrogates (e.g. in oncology, tumor shrinkage, progression-free survival; in diabetes, HbA1C levels in the blood)</td>
</tr>
<tr>
<td><strong>Health Economics and Outcomes Research (HEOR) Considered</strong></td>
<td>None (1)</td>
</tr>
</tbody>
</table>

Table 1 Notes: The many national, regional, and local payers in the EU each define HEOR and economic value differently. Some, such as the National Institute of Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) in the UK, focus on cost-effectiveness. Others, such as Haute Autorité de Santé (HAS), in France, and the Federal Joint Commission (G-BA) in Germany, concentrate on comparative clinical effectiveness. Other HTAs, such as the Spanish and Italian regional authorities, are most concerned with budget optimization and affordability.
<table>
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<tr>
<th>Date Introduced</th>
<th>Type of Early Advice Offered</th>
<th>Eligibility</th>
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<tr>
<td><strong>UNITED STATES</strong></td>
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| Early Consultation (Pre-IND, EOP1) | 1988 | • Pre-IND: review and reach agreement on design of animal studies; discuss key CMC issues; may touch on scope/design of Phase 1  
• EOP1: review Phase 1 safety data (sometimes preliminary efficacy data) and reach agreement on design of Phase 2 studies | For each new product or new indication studied in humans there is one pre-IND meeting available to sponsors (most advantageous for novel technologies and new or inexperienced sponsors) |
| Breakthrough Therapy designation (BT) | 2012 | • Intensive FDA guidance on efficient development plan, starting as early as Phase I  
• FDA commits senior managers and experienced review staff to application  
• FDA assigns cross-disciplinary project lead to review team to facilitate agency interactions | Treat serious or life-threatening condition AND preliminary clinical evidence indicates potential for “substantial” improvement over existing therapies on one or more clinically significant endpoints |
| **EUROPE** |
| Scientific Advice and Protocol Assistance | 2004 | • Advice on the number and design of appropriate tests and studies to conduct during development—available from EMA and from EU Member State National Competent Authorities (NCAs)  
• EMA provides written answers to questions posed by developers (the Scientific Advice Working Party [SWAP] may invite the sponsor to meet, if warranted)  
• Orphan products get protocol assistance | May be requested at any stage of development, whether the medicine is eligible for the centralized authorization procedure or not. Only orphan drugs are eligible for protocol assistance. |
| EMA/HTA Parallel Scientific Advice | 2010* | • Parallel scientific advice and protocol assistance from EMA and HTA bodies, including:  
• Early informal joint EMA/HTA discussions  
• HTA teleconference to discuss scope  
• 4-hr joint EMA/HTA evaluation meeting  
• Letter documenting CHMP regulatory scientific advice and written answers from HTA agency to sponsor’s questions | Parallel Scientific Advice is offered at any stage in the developmental lifecycle of medicines to provide prospective advice before the studies in question have started. Applicants may request advice from the EMA on any medicinal products for use in humans, but the eligibility criteria and scope of assessment may differ for individual HTA bodies based on their national/regional regulation and expertise. |
| Adaptive Pathways | 2014* | Development/evidence generation plan that allows for early, progressive patient access  
RWE is gathered to supplement RCT data  
Early involvement of patients and HTA agencies in drug development plan | Primarily for conditions with high medical need AND suitable for an iterative development pathway (e.g., CMA product or gradual expansion of target population) |
|------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Priority Medicines (PRIME) scheme | 2016 | Early dialogue to reinforce scientific/regulatory advice, and optimize development:  
CHMP Rapporteur appointed at proof of concept stage  
Kick-off development strategy meeting with multidisciplinary input from Rapporteur and EU network members/experts  
Iterative scientific advice at major milestones  
Access/pricing discussions with HTA bodies | New therapeutic option for condition with no current treatment options OR major therapeutic advantage over existing treatments AND preliminary clinical evidence indicating potential to produce significant benefits for patients with unmet medical needs and hence be of “major interest” from a public health and therapeutic innovation perspective |

**KEY TO TABLE 2 ACRONYMS:** CHMP: Committee for Medicinal Products for Human Use; CMA: Conditional Marketing Authorisation; CMC: Chemistry, Manufacturing and Controls; EMA: European Medicines Agency; FDA: Food and Drug Administration; HTA: Health Technology Assessment agency; IND: Investigational New Drug; MAA: Marketing Authorisation Application; RCT: Randomized Controlled Trial; RWE: Real World Evidence.

*first launched as pilot project.