Everyone knows it’s hard to get regulatory approval for a new drug; getting payer approval is becoming equally difficult. The key to success is to understand that regulators and payers will compare your product to others. Early-stage evidence reviews can help you differentiate your product from comparators on value. Later ones can provide the data needed to convince regulators and reimbursement agencies of that difference. Here’s how.
The road to receiving regulatory approval for a new treatment has always been long, expensive, and fraught with risk. Today, with payers assessing new product value more critically, achieving commercial success has become harder still.

Between 2000 and 2012, the FDA approved only 50 percent of new drug applications upon their initial submission. The reasons for rejection mainly were uncertainties related to dose selection, the choice of end points that "failed to adequately reflect a clinically meaningful effect," and poor efficacy when compared to the standard of care.¹

A PAREXEL analysis of reimbursement decisions of three agencies from 2005 to 2014 shows that 44 percent of new submissions received a negative review; 11 percent were restricted; and only 39 percent were deemed positive.

Another PAREXEL analysis² of rejections by the UK’s reimbursement agency (NICE) showed that their reasons for rejection were in descending order of frequency:

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These rejections can be catastrophic for drug developers. As the costs of development have risen, so has the price of failure. How can drug developers increase their chances of getting new products approved?

Any solution to this challenge must help differentiate a product from its competitors – and do so from the different perspectives of many stakeholders. A solution must address, among other things, the key stakeholders’ varying perceptions; how they might change over time; the history of guideline changes in a particular therapeutic area; whether treatment has ever included behavioral modification to improve outcomes; and the forms of treatment delivery that have improved outcomes and uptake.

An evidence review – a survey and analysis of data available in the public domain – is a powerful tool for achieving these ends. There is always information available; making the best use of it can help a company first find a way to differentiate its product, and then provide the proof of differentiation that regulatory agencies and payers are looking for.

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² “Exploring the Variability Between Disease Type and the Proportion of Submissions with ICERS Lower Than the Threshold That Are Rejected by HTA Agencies”, PAREXEL, 2014.
The data and insight gleaned from evidence reviews can uncover alternate strategies and inform critical decisions throughout the development process and beyond. Leveraging the fruits of these reviews can lead to differentiated positioning that addresses the needs of both regulators and payers and guides future clinical and commercial development.

INFORMING FUTURE CLINICAL AND COMMERCIAL DEVELOPMENT

Recently, PAREXEL conducted an evidence review for a client with a number of biologics for autoimmune diseases in its pipeline. The company wanted to understand the importance of immunogenicity to its pipeline portfolio to plan for future trials.

We conducted a systematic literature review (an SLR) of the evidence available on immunogenicity and its potential impact on the efficacy and tolerability of biologics across a range of major autoimmune diseases. We also assessed the clinical implications of immunogenicity on disease-specific efficacy parameters in both biologic-naïve and biologic pre-treated patients.

By conducting this review, we were able to show that the client’s interventions were less immunogenic than competing biologics (immunogenicity is an adverse effect of biologics), thereby providing their biologic with a differentiating advantage. This gave the client the confidence to advance to randomized control trials (RCTs) armed with the evidence on how to assess immunogenicity and support its case for bringing its biologic to market.

INFORMING TRIAL DESIGN

Evidence reviews can also inform and improve trial design itself. One of our clients was planning for clinical trials in rheumatoid arthritis (RA). They wanted (and needed) to understand the current key efficacy parameters for the disease, as well as the relationship between cognitive impairment and RA.

PAREXEL conducted a literature review that covered the effectiveness of current biologics in treating RA; the association between cognitive impairment and RA; and the scientific validity and clinical relevance of instruments that could be used to assess cognition for future trials of the client’s RA treatments. Using this information, the client was able to identify the most suitable instrument for measuring cognitive impairment and include it in its trials going forward.

CREATING A RISK MANAGEMENT PLAN TO MEET REGULATIONS FOR PHARMACOVIGILANCE

Almost all significant new treatments come with adverse effects, and all regulatory bodies demand pharmacovigilance activities to detect, understand, and prevent or mitigate them to whatever degree possible. Our client needed a risk management plan for the regulatory submission of a biosimilar. We conducted a systematic review using specific safety terms to gather the latest published evidence for the molecule, making sure that all the safety evidence was captured and incorporated into our report.

The client used the data we collected to help construct a risk management plan for submission, and because...

“...we were able to show that the client’s interventions were less immunogenic than competing biologics (immunogenicity is an adverse effect of biologics), thereby providing their biologic with a differentiating advantage.”
the searches were systematic, the report’s findings were reproducible and repeatable whenever the plan needed updating to incorporate any new information.

**COMMUNICATING PRODUCT VALUE TO HTA AGENCIES IN THE ABSENCE OF HEAD-TO-HEAD TRIALS**

One of PAREXEL’s clients had a drug in Phase III development and was targeting reimbursement submissions mainly in Europe. We helped support the submissions by conducting both an SLR and multiple treatment comparisons for the whole population and various subgroups within it. We used this review and consequent analyses to generate clinical effectiveness data for both global and regional economic models.

We also generated variance-covariance matrices to inform a probabilistic sensitivity analysis to assess how a change in a given parameter would affect those economic models. Using this evidence, the client was successful in communicating product value to reimbursement agencies.

**EVIDENCE REVIEW BENEFITS**

In the cases of the client looking to develop biologics to treat autoimmune diseases, and the client working to design RA trials for its new treatment, the evidence reviews PAREXEL conducted allowed them to go into primary research with fewer unanswered questions and, therefore, a better chance of success. The client developing autoimmune treatments already knew that the immunogenicity issues surrounding biologics were in its favor, and the client working on RA had a good idea of what would be the right instrument for measuring cognition. In each case the supporting evidence PAREXEL provided was critical both to the success of their trials and, ultimately, to their ability to demonstrate the value of their products to both regulatory agencies and payers.

The client developing a biosimilar, and the client already in Phase III, were both able to use our literature reviews and analysis to strengthen their regulatory and reimbursement submissions substantially.

Evidence reviews — whether they’re informal, addressing such early-stage objectives as trial design, or comprehensive, as for an HTA submission — draw on what’s already known about a compound, disease, delivery regimen, or therapeutic class. In other words, they make sure a company knows all it should know and all it can know about a drug throughout its lifecycle. These reviews can also identify any gaps in the evidence. They help companies make better decisions about which molecule to develop, which value strategies to pursue, and which trials to run. In so doing, they help pave the road to market and satisfy all stakeholders in their submissions.

**EVIDENCE REVIEWS CAN STRENGTHEN VALUE DIFFERENTIATION AND COMMUNICATION AT EVERY STAGE OF THE DEVELOPMENT PROCESS.**

- In Phase I, targeted reviews can inform clinical safety and dose assessment for the pharmacological class of interest.
- In Phases II/III, broader landscape assessment reviews can gather evidence on the efficacy and safety of comparators in the market, thereby informing trial design. They can also help determine which trial design parameters will best communicate differentiated value to regulators and payers.
- During the HTA submission period, systematic reviews can provide all the relevant evidence of clinical efficacy and safety of the molecule and its comparators to best communicate its value to the payers.
- Post-launch, focused positioning reviews can address safety regulations and inform benefit/risk evaluations.

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