As more companies develop drugs that treat orphan diseases and other unmet medical needs, patients and physicians are advocating for early access to them before they are approved, labeled, packaged and fully commercialized.

Positive early data, such as Phase II trial results, can ignite demand from patients and patient advocacy groups (PAGs) which is often fueled by social media. Patients with terminal or severely debilitating diseases, and no current treatment options, can’t wait for a drug to wind its way through the final one or two years of the regulatory process. These patients are not eligible or able to enroll in randomized clinical trials (RCTs).

Managed access programs (MAPs) offer companies an ethical, controlled and compliant way to distribute investigational products to the patients and providers who need and are demanding them. Doing so, however, can be complicated.

MAPS HELP PATIENTS BUT POSE PROBLEMS

MAPs can be time-consuming and expensive to administer with little perceived return on investment (ROI). Companies aren’t legally required to provide them and many don’t seriously consider them until late in development, when it’s too late to design an effective MAP program.

To make matters worse, peak demand for pre-approval access typically comes at a time when a company’s internal resources are maximally stressed: on the brink of a major regulatory submission. Thus, MAPs can pose serious challenges for developers, including:

• The lack of reimbursement [raising the cost of administering a MAP]

• Difficulty identifying eligible patients and treating physicians [beyond those asking for it] The need for speed in treating patients with urgent, unmet needs

• Planning for treatments in short supply or requiring special handling

• Fragmented regulatory requirements across countries and regions [see Table 1]

• Complying with local ethics committees and hospital procedures and policies

Most companies view MAPs as primarily a physical challenge, a test of the supply chain and distribution logistics. That’s short-sighted because MAPs offer an opportunity to collect real-world evidence and experience ahead of market launch. They can also provide a platform for building relationships with and educating physicians, patients and PAGs in the appropriate and safe use of a new product. All this has the potential to improve ROI by generating some revenue pre-approval and by providing data to support successful commercialization efforts down the road.

Companies can use MAPs to help patients while helping themselves. But how does one design and run an efficient, cost-effective MAP? Here are three lessons learned:
#1. INTEGRATE THE MAP INTO YOUR COMMERCIALIZATION STRATEGY

Very few companies spend the time and effort to integrate MAP planning and logistics with their commercialization strategy, but doing so is cost effective. A comprehensive commercial landscape assessment maps out a route to reimbursement country by country and should direct pre-approval access programs. Without such a roadmap, MAP logistics can swamp a company and overwhelm the commercial strategy.

The timing and order of global regulatory submissions is crucial to commercial success and may affect how MAPs are implemented. For example, an optimized product launch sequence in the EU often starts in Germany due to its free pricing policies for setting the list (originator) price, which serves as a reference point for other countries. Although Germany allows neither reimbursement nor extra data collection, a German MAP can still provide physicians with valuable early experience administering a new product. Such experience can increase post-launch uptake, demonstrate public health benefits and support the eventual list price.

For smaller companies, for which early ROI is critical, under certain conditions (for example, when a MAP runs in countries where companies can charge for a product), MAPS can even generate modest revenue or at least be cost neutral.

However, targeting countries that permit MAP reimbursement requires strategic thinking. What impact could a MAP price have on reimbursement negotiations post launch?

The United States and France both allow reimbursement, but differently. In France, if the MAP price is higher than the eventual commercial price, the company must refund the difference post-approval which requires that the company maintain a reserve fund. If the pre-approval price is too low, negotiating a higher commercial price later is difficult, if not impossible in France. In the United States, companies can only be reimbursed for the costs of production, shipping and administration of the product, which can be considerable for a biologic. Therefore, even a large company can benefit from making MAPs cost-neutral.

Finally, MAPs are not always the best way to support commercialization. The timing and suitability of a MAP is directly related to a drug’s risk-benefit ratio for patients and where it is on its development timeline. If a product’s safety or efficacy profile is substantially incomplete, a Phase IIIb trial may be a more efficient way than a MAP to collect trustworthy data that will support regulatory submissions.

#2. COLLECT REAL-WORLD EVIDENCE (RWE) TO SUPPORT REIMBURSEMENT AND PRICING

The requirements of regulators (product purity, safety and efficacy in a tightly defined set of patients) are different than those of payers who are looking for real-world outcomes and cost benefits. MAPs can offer companies the opportunity to bridge those differences with data collection mechanisms that are less expensive than RCTs but help strengthen the product value story.

Choosing useful—and even country- or population-specific—outcomes can demonstrate the real-world benefits of a drug, expand its safety database and reveal subpopulations or indications that should be studied formally. On a price per patient basis, collecting patient data in a MAP is about 25% of the cost of running an RCT.

PAREXEL recently advised a company with a targeted liver cancer drug on how to execute a MAP in selected European countries. In the EU, a fragmented set of local and regional reimbursement authorities are demanding more and better evidence of the patient value of new healthcare technologies. We recommended using the MAP protocol to fill RWE gaps that could support reimbursement from national payers. A study of recent coverage decisions by the UK’s NICE and Germany’s IQSWIG allowed us to identify the liver cancer outcomes that payers valued.

#3. INVEST IN TECHNOLOGIES AND PERSONAL RELATIONSHIPS TO MANAGE RISK

MAPs involve assuming substantial risks, including the risk of an underfunded or poorly executed program attracting negative publicity or damaging relationships with stakeholders. Of course, not doing a MAP is also risky: failure to provide access for patients to a needed treatment also can result in negative publicity and reputational damage. Companies can mitigate these risks by leveraging technology and working to build trust with patients and providers. For some, engaging a third-party contractor with expertise in administering MAPs is the best way to ensure a quality program.
Technology.

From the moment a patient qualifies through a MAP to receive medicine for a serious disease, the clock starts ticking. The right technology can enable rapid set-up and quicker response times which is critical when patients face a life-threatening disease, or the number of requests for a medicine is rising rapidly. Customized software running on a web-based platform can expedite responses without being hampered by the scalability and quality issues often met by overburdened teams.

Recently, PAREXEL designed a program that treated more than 11,000 patients and processed more than 26,000 compassionate use drug orders with a seamless scale-up. The configurable system allowed patients to register and receive an immediate response as to their eligibility in no more than 30 minutes (and often in as little as five), rather than wait for days for paper-based forms to be reviewed manually. Similarly, physicians were able to self-register and were guided through the workflow process by user prompts and notifications, saving them time and increasing accountability for compliance with paperwork requirements.

Relationships.

MAPs also involve quandaries that demand personal and face-to-face interactions, such as:

• How do you convince patients and physicians the MAP drug distribution decisions are fair, impartial and transparent? (If they doubt that, you’ve lost both potential customers and alienated key investigators for future studies.)

• How do you terminate a MAP once the product reaches market?

• How do you terminate a MAP if the product never reaches market?

Managing denials fairly and humanely is key to administering a MAP successfully and it’s a contingency for which many companies fail to plan. At PAREXEL, we convene teams of specialists to work with physicians on site. Such teams are needed for product launch in any case, but MAPs kick-start the process. These dedicated teams can educate physicians about the proper use of an experimental agent and explain eligibility criteria or safety issues that may arise.

MAP distribution and delivery snafus can produce damaging publicity. Social media can accelerate the spread of news and information throughout the healthcare system, from patient to patient and it raises and magnifies the risk of negative stories gaining credence. For example, one parent recently posted an online plea for an investigational cancer drug made by a large international pharmaceutical company that their child needed. Within 20 minutes, the parent had the phone number of the physician at the company administering the MAP and placed a call. Although the child was not eligible to receive the drug, the criteria were transparent and widely regarded as clear and impartial. Such stories highlight one of the risks of a poorly administered MAP: All it takes is one phone call to The New York Times for patients and providers – and then the public – to decry an unfair lack of access to a needed drug.

The best protection against negative publicity is a MAP that is well-planned and well-administered. Such a program can’t be thrown together at the last minute.

MAPS ENABLE COMPANIES TO DO WELL BY DOING GOOD

A well-executed MAP can provide life-changing benefits to patients. It can also confer competitive advantages because a MAP helps developers do the things they must do anyway but earlier and can convey additional benefits, such as:

• Building relationships with physicians, patients and PAGs that can facilitate commercial uptake and success

• Providing physicians with a chance to administer a new drug to a more heterogeneous set of patients than they can in RCTs, learning how it works best and how to give it safely

• Allowing payers an opportunity to evaluate the real-world benefits of the product

• For smaller companies with fewer human and financial resources, administering a MAP may generate modest early revenues or at least be cost-neutral while they retrieve its other benefits.

If the decision to run a MAP is made early enough, its provisions can be rolled into the overall development plan, improving the chances of success and increasing the expected ROI.
### TABLE 1. MANAGED ACCESS PROGRAMS (MAPS), COUNTRY BY COUNTRY

MAP is an umbrella term that covers an array of both vernacular and official regulatory terms that vary widely by region and by country:

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>AGENCY</th>
<th>SCHEME</th>
<th>INDIVIDUAL/COHORT</th>
<th>INITIATED BY</th>
<th>CAN COMPANIES CHARGE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>ANSM</td>
<td>ATU-cohort</td>
<td>Cohort</td>
<td>Sponsor</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATU-nominative</td>
<td>Individual</td>
<td>Physician</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>BfArM/PEI</td>
<td>AMHV</td>
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<td>EAMS</td>
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<td>Sponsor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specials</td>
<td>Individual</td>
<td>Physician</td>
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<td>AEMPS</td>
<td>Royal Decree 1015</td>
<td>Both</td>
<td>Physician</td>
<td>Can be negotiated</td>
</tr>
<tr>
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<td>AIFA</td>
<td>Law 648</td>
<td>Cohort</td>
<td>Physician</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uso compassionevole</td>
<td>Individual</td>
<td>Physician</td>
<td>No</td>
</tr>
<tr>
<td>Netherlands</td>
<td>MEB</td>
<td>Dutch Medicines Act-Article 40.3.f</td>
<td>Cohort</td>
<td>Sponsor</td>
<td>No</td>
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<tr>
<td></td>
<td>Health Care Inspectorate (IGZ)</td>
<td>Dutch Medicines Act-Article 40.3.c</td>
<td>Individual</td>
<td>Manufacturer, Wholesaler, Pharmacist</td>
<td>No</td>
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<tr>
<td>Canada</td>
<td>HC</td>
<td>SAP</td>
<td>Individual</td>
<td>Physician</td>
<td>Yes</td>
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<tr>
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<td>TGA</td>
<td>SAS</td>
<td>Individual</td>
<td>Physician</td>
<td>Yes</td>
</tr>
<tr>
<td>U.S.</td>
<td>FDA</td>
<td>Investigator IND</td>
<td>Individual</td>
<td>Physician</td>
<td>Yes – But only to cover for direct costs of making the drug available</td>
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<tr>
<td></td>
<td></td>
<td>Emergency Use IND</td>
<td>Individual</td>
<td>Physician</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment-IND</td>
<td>Cohort</td>
<td>Physician or Company</td>
<td></td>
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</tbody>
</table>

**NOTES:** There are two traditional types of MAPs, Individual and Cohort. An Individual (aka “Named Patient”) MAP is essentially a compassionate use program for individual patients and it is typically physician-initiated. A Cohort MAP is for a defined patient group and is usually manufacturer-initiated. Some countries have only Individual MAPs; some have Cohort MAPS; some have both.