UNMET NEED IS THE SINGLE MOST IMPORTANT FACTOR IN ACCESS, BUT PAYERS' AND COMPANIES' DEFINITIONS ARE VERY DIFFERENT.

GUEST COMMENTARY: PRODUCT DEVELOPMENT

DEFINING ACCESS POTENTIAL – BEFORE IT'S TOO LATE

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We see it everywhere: confirmation bias.

Innovators believe in a drug, find the evidence to support its value, and dismiss or ignore the facts challenging their preferred story.

But confirmation bias is particularly problematic thanks to reimbursement — a market-maker still unfamiliar to the majority of drug developers. Its arcane rules, logical inconsistencies ("Saving money in two years — fine. Saving a lot more, but over five years — not fine,") and Rube Goldberg structure of influencers make it far easier for execs to assume reimbursement success will follow clinical value, defined in the relatively narrow way traditional in the biopharmaceutical industry, and leave it at that.

It's a dangerous assumption.

Industry and its investors need a clear, objective lens through which they can burn away confirmation bias and see the likely access barriers their drugs will face once approved.

Had such a lens been applied to 2017 launches like Regeneron Pharmaceuticals Inc.'s Dupixent dupilumab or Radius Health Inc.'s Tymlos abaloparatide-sc, investors wouldn't have been as surprised at their commercial challenges. Nor would they have been surprised on the upside by the breakout success of AbbVie Inc.'s Mavyret glecaprevir/pibrentasvir.

The questions for investors and companies are: Which drugs will payers want, and be able, to restrict? Which ones will get a pass? And once that's figured out, what do the manufacturers do to maximize the commercial potential of these products?

As an example of how to systematically apply an access lens, we designed an algorithm called Access Meter that incorporates the roughly two dozen elements that would either block or allow patients access to a drug with at least relatively generous reimbursement (see Sidebar: "Behind the Access Meter Scoring").

Applied to a handful of 2017 launches, we found scores did generally correlate with performance.

More importantly, among drugs launched or likely to be launched in 2018, Access Meter scores show that drug companies have a lot of work to do to solve the access conundrum.

A number of drugs will meet relatively few challenges; a larger handful will see some, but not insurmountable, hurdles; and the remainder will require highly sophisticated payer strategies to meet their investors' expectations.

One overwhelming conclusion: unmet need is the single most important factor in access, but payers' and companies' definitions are very different.

The challenge for companies commercializing drugs is to figure out how to capitalize on their access advantages and mitigate their disadvantages. Moreover, they need to anticipate that the access pluses and minuses will change as more clinical evidence arrives, as prices rise or fall, as competitors are approved, and as payers flex more muscle in specialty areas where they were once afraid to go.

LAGGERS AND LEADERS

At both ends of the spectrum, the Access Meter scores correlate with commercial performance for drugs launched in 2017.

For example, Trulance plecanatide, the chronic constipation drug from Synergy Pharmaceuticals Inc., and Radius' Tymlos for osteoporosis, struggled commercially.

Trulance sales, a disappointing $16.8 million in 2017, fell in 1Q18 — not the expected performance of a drug in growth mode.

Tymlos was similarly challenged, with just $12.1 million in 2017 sales in a multibillion dollar category. Its strategy to gain share has been to cut price, but it has yet to deliver a big bump in sales. The price cut did allow Tymlos to replace Eli Lilly and Co.'s Forteo teriparatide on the Express Scripts Holding Co. formulary.

Synergy and Radius have both seen significant stock slides since the drug launches. Synergy is down over 70% since Trulance was approved in January 2017, and Radius has lost almost 25% of its share price since the April 2017 approval.

Trulance and Tymlos ranked in the bottom of the range in the Access Meter review, weighed down by poor scores, most importantly in payer-defined unmet need.

They had few counterweighing advantages. They were not in any protected classes — drug classes or indications in which Medicare requires Part D plans to include virtually all approved medicines — and by our assessment, were not particularly novel from a payer's point of view. Nor did we think they demonstrated clinical differences that payers would be required to recognize with more generous access policies (see Figure: "Access Meter Scores")

At the other end of the spectrum, AbbVie's hepatitis C therapy, Mavyret glecaprevir/pibrentasvir, and Neurocrine Biosciences Inc.'s Ingrezza valbenazine, for tardive dyskinesia, have significantly outperformed most investors' expectations.

Sales of both drugs have rocketed up – $116.6 million for Neurocrine in 2017 on eight months of sales and another $71.1 million in 1Q18. Its stock has mirrored its sales, more than doubling since the approval.

Mavyret has effectively stolen the hepatitis C market from Gilead Sciences Inc. It now has roughly half of all new prescriptions, helped by its price, which is significantly lower than even the post-rebate cost of Gilead's Harvoni ledipasvir/sofosbuvir. But since Mavyret also allowed virtually pan-genotypic use, there was no reason to continue to prefer Gilead's drug.

SCORING FUTURE ACCESS

Of course, a drug's access potential can no more be reduced to a single number than a baseball player can be reduced to a batting average or on-base percentage.

The Access Meter score is a guide, subject to change with new evidence. A score does not define a drug's commercial fate. Companies can hobble a high scorer with a clumsy market access approach, or improve a low scorer's prospects with a strategy that works for payers, such as value-based contracting.

Among the high scorers for drug candidates launched or expected to be launched this year is brexanolone, a first-in-class GABA A modulator for treating postpartum depression (PPD) from Sage Therapeutics Inc.

Brexanolone serves a high unmet need — it would be the first approved drug for treating PPD. As a single infusion, it has a very limited duration of therapy, which means that payers wouldn't be paying for the drug year-in and year-out.

The drug wins additional points for getting FDA breakthrough status and for its status as a medical-benefit drug, which makes controlling access more difficult for payers. Sage would also benefit from strong support by effective women's health patient advocacy groups because payers are wary of the negative press these groups can generate.

Brexanolone might still face some access challenges. It's a potentially expensive new therapeutic in a category with thus far insignificant drug costs.

Not only does that mean payers would be passing on additional expense to their employer clients (absent recognizable and quantified cost-offsets), it also means they would have no good yardstick for forecasting the total cost impact of the drug. Nor could they be certain about value for money.

In particular, payers will be worried that the drug will get widespread use in populations where it hasn't shown its greatest value.

The drug works most dramatically in severe PPD patients, who hit the three-point change in the Hamilton Depression Rating Scale (HAM-D) that guidelines from the National Institute for Health and Care

BEHIND THE ACCESS METER SCORING

Access Meter is a quantitative tool Real Endpoints LLC uses to define the access potential of pipeline candidates.

The algorithm behind the tool uses roughly 20 elements, each of which is weighted in importance relative to the others. The higher the total score for the drug, the lower the access hurdles – that is, the more trouble a payer will have in restricting the drug's use.

Criteria include:

– unmet need (a payer's understanding of competitive intensity in the indication)

– a unique mechanism of action (importantly, unique in the eyes of the payer)

– the current and likely near-term competitive density

– obvious cost-offsets

– whether it's a cancer drug

– whether it's a cure

Using multiple criteria creates a more nuanced picture of the access challenges and opportunities. For example, Waylivra volanesorsen from Akcea Therapeutics Inc. scores well on unmet need and prevalence but will face competition from unapproved drugs, notably the plethora of generic statins. Waylivra is in registration to treat the rare disease familial chylomicronemia syndrome (FCS). Payers may make patients step through different statins before they're given access to Waylivra. The algorithm captures the generics consideration and modifies Waylivra's score accordingly.

— JANE BORNE AND ROGER LONGMAN

Excellence cite as clinically meaningful. While it could be approved for moderate PPD patients, who showed some improvement, that cohort didn't hit the three-point mark. Another uncertainty we weighed was whether Sage's 30-day trial was long enough to prove durability of effect.

Olumiant baricitinib is among the 2018 drugs with low Access Meter scores. It is approved for rheumatoid arthritis (RA), from the partnership between Lilly and Incyte Corp.

The oral JAK inhibitor is entering a crowded market, although its only major oral competitor is Pfizer Inc.'s Xeljanz tofacitinib, another JAK inhibitor.

We consider RA a particular challenge for new competitors: payers make huge rebates off current injectable drugs like AbbVie's Humira adalimumab and Amgen Inc.'s Enbrel etanercept. Payers will be loath to put any new competitor into a preferred position if it means forgoing rebate revenue.

Also, FDA slapped a black box warning for blood clots on the Olumiant label and approved only the less efficacious 2 mg dose. Physicians will not likely push hard against those restrictions.

Lilly hopes to carve out some payer market share for Olumiant by pricing the drug at half Xeljanz's cost. But given the rebate dollars at stake, that may not help much.

Moreover, Olumiant faces a patent problem: Xeljanz could lose its exclusivity in 2020, which is barely enough time for Lilly to gather data that might lay Olumiant's safety concerns to rest. And payers can't be expected to switch patients to a branded drug when its competitor is about to go generic.

THE ONCOLOGY CONUNDRUM

From an access point of view, oncology seems like a no-brainer.

As a Medicare protected class, it has unique reimbursement traditions. For example, for a particular indication, if an oncologic is listed as a useful therapy in one of the approved compendia, such as in the National Comprehensive Cancer Network (NCCN) guidelines, then payers generally reimburse for it.

But things are changing from the payer's point of view, particularly with oral drugs not filling a significant unmet need.

For example, in prostate cancer, Johnson & Johnson's Zytiga abiraterone won exclusivity on the CVS formulary. That means patients can only get reimbursed for Xtandi enzalutamide, from Astellas Pharma Inc. and Sanofi, through an exception process.

Moreover, oncology is also being affected by another access hurdle from a different category of payers: patients.

The higher the patient portion of the cost, the more patient abandonment – i.e., the worse the access. For relatively undifferentiated oncologics, this is a growing problem, and one that will likely mean discounting.

One example is Array BioPharma Inc.'s Braftovi encorafenib/Mektovi binimetinib, which is a combination of oral medicines for melanoma that does not appear to be a major improvement over Novartis AG's Tafinlar/Mekinist combination.

In the Phase III COLUMBUS trial in patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, Braftovi/Mektovi had a median progression-free survival (PFS) of 14.9 months vs. 7.3 months for the BRAF inhibitor Zelboraf vemurafenib. The competitor Tafinlar/Mekinist had a median PFS of 11.4 months vs. 7.3 months for Zelboraf in the Phase III COMBI-v trial in patients with BRAF V600E or V600K mutation-positive unresectable or metastatic cutaneous melanoma.

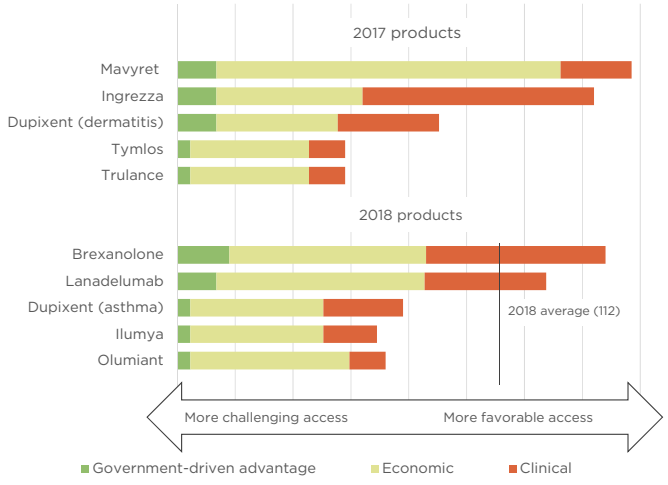
Indeed, on the Access Meter, Array's product scores on the low end of the range for oncologics. Thus it should not come as a surprise that Array is offering a significant discount to patients, the payer category most likely to create an access hurdle.

ACCESS METER SCORES

TOP: Higher scores from Real Endpoints LLC's Access Meter for drugs launched in 2017 generally correlated with higher sales. Mavyret glecaprevir/pibrentasvir boosted 1Q18 U.S. sales of the HCV franchise for **AbbVie Inc.** (NYSE:ABBV) to $343 million from $38 million in 1Q17. It was approved in late August. Ingrezza valbenazine, which **Neurocrine Biosciences Inc.** (NASDAQ:NBIX) launched on May 1, 2017, had $161.6 million in 2017 sales and $71.1 million in 1Q18. Dupixent dupilumab from **Regeneron Pharmaceuticals Inc.** (NASDAQ:REGN) and **Sanofi** (Euronext:SAN; NYSE:SNY) had 2017 U.S. sales of €216 million ($259 million) and 1Q18 U.S. sales of €95 million ($114 million). **Radius Health Inc.** (NASDAQ:RDUS) reported 2017 sales of Tymlos abaloparatide of $12.1 million and 1Q18 sales of $14.5 million; it launched the osteoporosis drug last May. **Synergy Pharmaceuticals Inc.** (NASDAQ:SGYP) reported 2017 sales of Trulance plecanatide of $16.8 million and 1Q18 sales of $6.8 million. FDA approved Trulance for chronic idiopathic constipation in January 2017.

BOTTOM: Access Meter scores for selected products approved or anticipated in 2018 are shown in the bottom chart. An NDA from **Sage Therapeutics Inc.** (NASDAQ:SAGE) for brexanolone to treat postpartum depression has a Dec. 19 PDUFA date. The BLA for lanadelumab from **Shire plc** (LSE:SHP; NASDAQ:SHPG) to treat hereditary angioedema has an Aug. 26 PDUFA date. Both have Priority Review. The sBLA for Dupixent to treat moderate-to-severe asthma has a PDUFA date of Oct. 20. In March, FDA approved Ilumya tildrakizumab-asmn from **Sun Pharmaceutical Industries Ltd.** (NSE:SUNPHARM; BSE:524715) to treat plaque psoriasis. FDA approved Olumiant baricitinib, from **Incyte Corp.** (NASDAQ:INCY) and **Eli Lilly & Co.** (NYSE:LLY), in June to treat rheumatoid arthritis.

Source: Real Endpoints LLC, company earnings statements



Array is offering a $0 co-pay, up to a $25,000 maximum. Novartis offers a $20 co-pay up to $15,000 for its combo. Oncology, in short, is no longer immune to price competition – and an objective scoring system like Access Meter can show why.

REAL-WORLD VALUE-FOR-MONEY

Companies with drugs that score higher on the Access Meter may have an easier time getting access for patients than those with lower scoring drugs, but every manufacturer will still have to figure out a way of defining value for money in its commercial strategies.

THE CHALLENGE FOR COMPANIES COMMERCIALIZING DRUGS IS TO FIGURE OUT HOW TO CAPITALIZE ON THEIR ACCESS ADVANTAGES AND MITIGATE THEIR DISADVANTAGES.

Sometimes such strategies will involve a value-based or risk-sharing contract; sometimes a value-based pricing initiative; sometimes a program that discounts a drug or limits its use until the manufacturer makes the real-world evidence available to justify its use; sometimes a combination.

Each will work in some cases and not in others. None is without risk and complexity, and none should be considered in the absence of the others.

But in all cases step one for companies is to understand how these payer customers determine value, which in turn requires understanding the criteria by which payers determine access.

In our experience, most companies don't objectively review these criteria. Often senior R&D executives don't know the criteria and, for various bureaucratic reasons, don't listen closely enough to people in their companies who do.

Instead, with portfolio decisions made and development strategy set, confirmation bias entrenches itself, further cemented by the sunk cost fallacy — and the drug is ultimately launched into a market with neither the data nor the strategy that gives the buyer the incentives to support it.

The antidote to this commercially destructive process is the objective appraisal of value from the payer's point of view — of which at least one element is defining access potential. It's not impossible, as Access Meter shows, to do this before critical development and commercial strategies are set. The challenge for companies is whether they've got the intestinal fortitude to listen to the results. bc

— Real Endpoints is an information and analytics company focused on pharmaceutical reimbursement.

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), North Chicago, Ill.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Array BioPharma Inc. (NASDAQ:ARRY), Boulder, Colo.
Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Express Scripts Holding Co. (NASDAQ:ESRX), St. Louis, Mo.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Incyte Corp. (NASDAQ: INCY), Wilmington, Del.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Neurocrine Biosciences Inc. (NASDAQ:NBIX), San Diego, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Radius Health Inc. (NASDAQ:RDUS), Waltham, Mass.
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Sage Therapeutics Inc. (NASDAQ:SAGE), Cambridge, Mass.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Synergy Pharmaceuticals Inc. (NASDAQ:SGYP), New York, N.Y.