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Real-World Evidence And The Quest For European Market Access

by Francesca Bruce

Real-world evidence promises to solve many problems inherent in getting a drug to patients at a good price. It could slash development costs and help make the reimbursement case to payers. But there are challenges for companies that want to exploit real-world evidence to get their drug to patients in Europe.

- Real-world evidence has the potential to help companies get drugs to patients more quickly by altering pharma's R&D paradigm.
- RWE is likely to become a more important means of proving the value of medicines to payers, thus improving the odds of getting reimbursement.
- Adoption has been slow, but increased digitization of real-world data sources should encourage more usage.
- Pharma companies face a number of challenges in successfully exploiting RWE, such as poor data quality and security concerns.

Getting an innovative new drug to patients and convincing payers to pay a good price is no easy feat, as pharma companies know. Real-world evidence has for some time been touted as a remedy for quicker approvals, better discussions with payers and flexible reimbursement agreements. Even though advances in digitization mean that data are potentially much more accessible, real-world evidence has yet to fulfill its promise. A lack of trust in what will happen to patient data, poor approaches to market access and concerns over whether the data are fit for purpose are just some of the challenges in Europe.

Cash-strapped payers are balking at the prices of many pharmaceuticals and thinking hard about whether they want to pay. Real-world evidence originating from, for example, patient registries, electronic health records, claims data or observational cohort studies is likely to become an

increasingly important means of proving the value of medicines to payers. *Janssen Pharmaceuticals Inc.*'s Nigel Hughes, scientific director, RMEDS (real-world evidence, medical affairs, established products, statistics), believes RWE makes good business sense. "Understanding real-world experience and outcomes is critical to ensuring we provide safe, efficacious products to our patients in any given market ... and getting excellent outcomes for patients and demonstrating the real-life value of those outcomes to stakeholders is key to the firm's business success," he says. "RWE offers the possibility of gaining greater insights into potential opportunities for new products, and/or product extensions, service development and cost efficiencies, including study optimization," he adds. Service development and "attuned approaches" to a common understanding of how to re-engineer health care provision of efficacious products are further possibilities," he adds. *(Also see "Q&A: Janssen on where it is heading with real world evidence*" - Pink Sheet, 20 Oct, 2016.)

RWE has been around for some time supplementing marketing authorization applications and pricing and reimbursement files. Although no silver bullet, Anke van Engen, a principal at QuintilesIMS, says that RWE does improve the probability of winning reimbursement. "An analysis using data in our *HTA Accelerator* platform showed that inclusion of RWE in France was associated with higher benefit ratings," she says. Meanwhile, in England, the health technology assessment (HTA) body, the National Institute for Health and Care Excellence (NICE) recently changed its mind and decided to recommend *Johnson & Johnson*'s *Zytiga* (abiraterone acetate) for chemotherapy-naïve metastatic castration-resistant prostate cancer patients after J&J presented real-world evidence from US insurance claims data.

The promise of future real-world evidence is also an influencing factor on decision making. Many managed entry agreements or risk sharing deals in Europe rely on the gathering of real-world data (RWD). In France, for example, *Celgene Corp.*'s *Pomylast* (pomalidomide) for multiple myeloma is reimbursed under a risk sharing scheme, which will see the company repay the cost of the drug if the patient does not respond to treatment. Payers were uncertain about whether a modest extension of progression-free survival would translate into much benefit in the real world. Risk sharing schemes are also common in Italy to secure reimbursement of cancer treatment, and registries track outcomes. In Spain, Catalonian authorities are experimenting with managed entry agreements that will rely on data gathered from registries. England's Cancer Drugs Fund essentially offers conditional reimbursement for expensive cancer drugs backed by limited evidence, and the gathering of real-world data can make up part of the evidence package for companies wanting to prove their case. Sweden's HTA, the TLV, takes a value-based pricing approach. "The price has to reflect the value created when the pharmaceutical product is used. That means that real-world data directly or indirectly showing the value of the use of a product is of large interest to TLV," says Niklas Hedberg, the TVL's chief pharmacist.

The Salford Example

Digitization and the advance of electronic health records makes the analysis of real-world data

easier as sources become less difficult to mine. Sweden's TVL says the advance of digital records there has been a very important development. However, digitization is moving at different speeds across Europe. The UK has so far made the greatest strides, while progress has also been made in the EU5, the Nordic countries and other markets, including Estonia. *GlaxoSmithKline PLC*'s groundbreaking Salford Lung Study was only possible because Salford, in Greater Manchester, UK, was a "truly paperless" center that had had for some time an integrated e-health record system shared between primary and secondary health care, says David Leather, MD, GSK's global medical affairs leader in the respiratory franchise, who led the UK-based study. *(Also see "Real-World Evidence: Lessons From GSK's Salford Lung Study*" - Pink Sheet, 9 Sep, 2016.)

This study, which began in 2013, is the first ever prospective randomized control trial (RCT) in an everyday health care setting. It set out to compare the effectiveness of *Relvar/Breo Ellipta* (vilanterol/fluticasone furoate in a dry-powder inhaler) with existing therapies for COPD and asthma over a 12-month period in a real-life setting. To ensure patients experienced a minimum of interference from the trial, data were gathered from electronic health records that were updated every time a patient within the trial came into contact with the health care system, including general practice, attendance and emergency center (A&E), pharmacy and out-of-hours services. The study was open label and had a broad population of eligible patients with minimal exclusion criteria, ensuring the population was much more representative of the patients who would take the medicine in real life. Results from the COPD arm showed a significant 8.41% lower rate of exacerbations between Relvar and the standard of care ($p = 0.025$). GSK will release results from the asthma arm in 2017.

GSK's twice-daily inhaled corticosteroid/long-acting beta-agonist inhalers *Advair/Seretide* (fluticasone/salmeterol) are facing generic competition and the company will be keen to see patients moved on to Relvar. According to Leather, the firm hopes that the Salford Lung Study will positively inform payers, guideline writers and clinicians. However, the jury is still out. As Leather explains, GSK is the first company to produce such evidence. "A lot of people were unsure what the data would look like, but now we have a quality analysis of a substantial database that is now with groups like regulators and guideline writers. Their evidence hierarchies don't include this type of evidence and now they have a data set they can make sense of and decide what it means." He believes the study is an evolution rather than a revolution in the development of real-world evidence that will help the field move forward. "It isn't just about what the industry produces. It is also about the value people ascribe to it; people haven't had the chance to evaluate data like this because it has so far not existed. There has been massive interest and I think it is going to trigger an evolution in thinking. That won't just be driven by industry but also by the people who receive the information and make sense of it."

GSK is gathering health care resource utilization data that could potentially highlight savings made elsewhere in the health system. "If a company has a new antibiotic that was incredibly expensive, it would want to show that actually by using that expensive antibiotic at a certain point in the care, the system would actually save money." – Marie Kane, NorthWest EHealth

Beyond effectiveness, the Salford Lung Study is also important because it aims to show payers what financial impact the drug may have on the health system. GSK is gathering health care resource utilization data, which tracks costs for health care authorities. The findings will be published at a future scientific meeting, according to the company. The firm says it is the first company to produce such evidence and that it hopes it will offer a "wealth of information" on disease management to help decision makers. Such data could be incredibly powerful and could highlight savings made elsewhere in the health system, says Marie Kane, chief operating officer of NorthWest EHealth, which developed the technology platform necessary for the Salford Lung Study. "If a company has a new antibiotic that was incredibly expensive, it would want to show that actually by using that expensive antibiotic at a certain point in the care, the system would actually save money."

New R&D Paradigms?

The regulatory burden that companies developing innovative drugs face is a big one, and the R&D model is fast becoming unsustainable. The path to authorization is expensive and often littered with failures, whereas randomized controlled trials, the gold standard for gathering the necessary data, are costly and time-consuming. But with real-world evidence, there is potential to do things differently, resulting in lower costs and earlier approvals. The sooner a drug is approved, the sooner it can start to recoup investment and make a profit, and while the drug is on the market, it is protected by a patent, says Kane. She believes that a trial like the Salford Lung Study, a late Phase III trial, could actually be done at late Phase II. "It would give companies the capacity to sail sooner, and therefore not waste as much money. I think it would potentially enable adaptive trial design because you are getting the data in an almost live format. You can do monthly reviews of data logs to see what is happening with outcomes." Kane points to the possibilities in oncology: "If group A of patients with this particular phenotype is responding to drug A, but group B with a different phenotype isn't, you could take group B off the drug and keep group A on it. This potentially could shorten the whole trial lifecycle and therefore get your drug to market quicker."

Faster approval means fewer development costs, which could lead to a price that is more attractive to payers. Rafaat Rahmani, CEO of Lifescience Dynamics, believes that in the not so distant future companies will invest less in RCTs and think about alternative research paradigms, with a number of drivers forcing them to think differently. Companies want to get to the market quickly, he says. "The first, second and third to market products are the ones that share the market, the fourth or fifth tend to have a small market share, so the earlier you get to market, the better overall." It is early days, but the potential for real-world evidence to drive change in R&D is acknowledged by different authorities and already initiatives featuring elements of real-world data collection are underway. For example, the European Medicine Agency's Adaptive Pathways is a "concept" for developing medicines and generating data in order to allow patients earlier access to innovative medicines, largely in areas of great medical need where traditional means of collecting data would be difficult. (*See sidebar, "RWE: The EMA's View."*)

RWE: The EMA's View

By Francesca Bruce

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The European Medicines Agency outlines the difficulties that impact regulators' ability to access and analyze real-world data.

Read the full article here

Strategies May Shift

To really harness the power of real-world evidence, some companies may need to think differently and take a second look at their internal structures. Hassan Chaudhury, chief commercial officer at UK-based data consultancy Health iQ, believes that the marriage between market access and RWE is not as mature as it should be. Part of the problem, he says, is that some companies understand market access better than others. Whereas some think of it as simply getting a product on a formulary, others see it as a bigger process in which all functions in a company are aligned, and as an opportunity to create a better environment in which to sell. In addition, many company teams, he says, work in isolated silos. Market access should touch all functions in a company, including real-world evidence. He believes that a combination of GSK, which has an "excellent" approach to RWE with its own specialized in-house team, and *Roche* would be a good model. The Swiss firm operates an integrated franchise committee that ensures all the different teams working on a brand, including health economics outcomes research, market access and research, are all aligned and unified on what they are trying to achieve for the brand.

Meanwhile, QuintilesIMS' van Engen thinks that every company should have an RWE strategy that should span a product's entire lifecycle and that should "anticipate stakeholder needs." (*See box.*)

Numerous Challenges Remain

Even with a good strategy in place, companies will face numerous challenges. RWE studies can be expensive – the Salford Lung Study cost GSK around £80 million to conduct, which it says is broadly in line with the cost of a large traditional RCT. Many companies will be reluctant to spend this amount of money and will try to use existing real-world data sources. But most sources of RWD are not collected for research purposes, which means data quality is an issue. In addition, methods of addressing data gaps and inconsistencies are not yet widely accepted for statistical validity. It is therefore not surprising that HTA bodies can be slow to accept evidence from real-world sources. "Randomized control trials are always our gold standard, other types of evidence serve to supplement this," says NICE. "The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and end point occur more commonly in non-randomized studies and non-controlled trials than in RCTs," the institute says in its methods guide for technology appraisals.

Sweden's TVL finds that selection bias is a problem and is calling for solutions, say Hedberg. He also advises companies to correlate RWD to a baseline to show a value for the health development of the standard population, and respond to questions relating to pricing and reimbursement. Early planning and early dialogue with stakeholders is key to make sure companies get their approach right. Data validation can be a big task, but a good analyst will ensure it is robust, says Lifescience

QuintilesIMS' RWE Strategy, Nine Key Tips

1. Start planning early on in late Phase II or early Phase III.
2. Simultaneously set up a centralized, but locally informed, decision-making and funding process for real-world research. A purely centralized process may miss critical local needs. A highly localized process can be inefficient and less impactful.
3. Because treatment landscapes and payer needs change, firms must also re-evaluate the process at every development milestone.
4. Start with "insight generation," which includes understanding what data are needed and when, how its value is defined and how it will be used.
5. When the research question is clear, the next step is an evaluation of real-world data sources to enable the elaboration of the research approach.
6. Don't try to fill every gap in the evidence. And be aware various levels of evidence are required for impact.
7. Get input from the external stakeholders in key countries to ensure the plan can be implemented both at a global and local level.
8. Prioritize biggest concerns expressed by external stakeholders.

Dynamics' Rahmani. "You need to say how the data were captured, show whether there was any opportunity for error, alteration, bias or to manipulate the data."

Van Engen suggests hybrid designs, for example using retrospective data to inform the design of a prospective real-world study. Chaudhury points to the analysis of Hospital Episodes Statistics (HES), available in England, which he says is one of the best data sets in the world. The data track hospital admissions and gives detailed information such as the reason for admission, the length of stay, and whether the patient was admitted to A&E. With these data it is possible to point to trends and have a discussion, Chaudhury says. For example, a company might show a payer HES data analysis revealing that COPD admissions are going up alongside prescribing data that show prescriptions of a certain COPD product are falling. "This is not a study, this is a trend. But that is what you can do with real-world data, you show what is happening to really drill down, and based on that information, you can do clinical trials or a study or an audit. The real world is about touch points and clinicians like evidence from sources that they can see."

Consider using a range of study designs from surveys to pragmatic trials for greater impact on decision makers, including regulators, payers, providers, prescribers and patients. No single study is sufficient to address a priority issue.

Source: Anke van Engen, a principal at QuintilesIMS Consulting Services

Trust is another issue. Janssen's Hughes points out that people will donate organs but are more reticent about sharing personal data. "The industry has been challenged in terms of trust and perception with the general public. I can understand that; we haven't exactly covered ourselves in glory in the past." He says the solution is for companies to be open, honest and transparent about anything they are proposing to do and be very clear about the intended use. Hughes believes that industry, regulators and the general public need a much broader debate about how technology is changing the world. "All sorts of stakeholders need a say in how we manage and access this data for the better for society. I don't just mean about new drugs but how we can manage disease better, or see if there are better ways of managing it."