**Introduction**

The use of real-world evidence (RWE) is exploding across the pharmaceutical and clinical arenas, adding value at every stage of the pharmaceutical life cycle. The COVID-19 pandemic and its enormous impact on our medical systems has accelerated the growth in and adoption of RWE. To stimulate a conversation about the current state and future of RWE, *Pharmaceutical Executive*, in collaboration with Parexel, brought together leaders in pharmaceutical development and clinical applications for a roundtable discussion. The expert panel, which convened remotely in September 2020, included:

- **Host**: Peyton Howell, Executive Vice President, Chief Commercial & Strategy Officer, Parexel
- **Guest Speaker**: Scott Gottlieb, MD, Former Commissioner of the Food and Drug Administration (FDA)
- **Moderator**: Sy Pretorius, MD, Chief Medical and Scientific Officer, Parexel
- **Facilitator**: Lisa Henderson, Editorial Director, Pharmaceutical Executive
- **Marc Berger**, MD, Consultant
- **Amanda Bruno**, PhD, MPH, Vice President and Head of RWE Oncology, Bayer
- **Mark De Rosch**, PhD, Chief Regulatory Officer, Epizyme
- **Riad Dirani**, PhD, Vice President Global HEOR, Teva
- **Ajit Ganguli**, PhD, Senior Director, Head of Oncology, Global HEOR, Astellas
- **Chris Garabedian**, Chairman and CEO, Xontogeny
- **Nuwan Kurukulasuriya**, PhD, Senior Vice President and Head, Global Medical Affairs, MorphoSys
- **Leanne Larson**, Senior Vice President and Worldwide Head, Real-World Evidence and Access, Parexel
- **Charles Makin**, MS, MBA, MM, Global Head, Medical Health Outcomes Research, Biogen
- **Amy McKee**, MD, MBA, Global Head, Medical Health Outcomes Research, Biogen
- **Mats Rosenlund**, PhD, Vice President, Global Head of RWE, RWD and Analytics, Daiichi Sankyo
- **Gregg Sylvester**, MD, MPH, Chief Medical Officer, Seqirus
- **Simu Thomas**, PhD, Vice President and Global Head HE&OR, Alexion Pharmaceuticals
- **Bill Tubbs**, Head of Regulatory Affairs, Visterra, Inc.
Special guest Scott Gottlieb, MD, former FDA Commissioner, an advocate for advancing the health of patients, promoting healthcare access, and driving innovation, kicked off the discussion with an overview of the landscape. Under his leadership, the FDA implemented reforms to standardize drug reviews and made historic improvements on post-market data collection and the use of RWE.

Opening Remarks from Former FDA Commissioner: Current State and Future of RWE

The COVID-19 pandemic has created the need and the opportunity to increase and solidify the collection and use of RWE, said Gottlieb in his opening remarks to the panel. The past seven months of the pandemic, he stated, "reinforces the importance of having practical information to help guide decision-making across the spectrum in healthcare. And, it helps accelerate some of the adoption curves around the use of real-world evidence."

Gottlieb pointed out several ways that RWE is especially useful in situations like the pandemic, where traditional randomized trials are impractical because the need for therapeutics and vaccines is so immediate.

1. **Post-market data collection.** When a vaccine is ultimately approved, likely under FDA’s Emergency Use Authorization (EUA) authority, RWE will provide flexibility for very active post-market safety and effectiveness data collection on the initial cohorts of patients, as well as continued collection of prospective effectiveness and safety data to inform dosage and other decision-making.

2. **Regulatory decision making.** On the therapeutic side, RWE has been an important factor in making decisions about patient care during the pandemic on the basis of large datasets. For instance, plasma therapy as a treatment for COVID-19 is a prominent area where the healthcare community looked at various cohorts of patients (e.g., those receiving a low dose of antibodies in the plasma versus those receiving a higher dose) within a large practical dataset to make judgments about efficacy, said Gottlieb.

3. **Clinical development.** Gottlieb also touched on a third area where the pandemic spurred greater collection and use of RWE. "You’ve seen a lot of amendments to [clinical trial] protocols where there have been missing data—such as from patients lost to follow-up—and sponsors have been able to use RWE to augment the datasets that were already being accrued, to compensate for some of the complexities that were created by COVID such as not being able to bring patients back onsite for follow-up," he noted.

4. **Accelerated clinical learnings.** Gottlieb also made the point that there have been substantial improvements in the clinical care of COVID patients in a relatively short period of time, including using anticoagulation medications more readily, intubating patients less aggressively, keeping patients better hydrated, and understanding the benefits of steroids in these settings. "Some of these learnings, these improvements in care, derive from formal trials... but a lot of these other things really derive from large, practical datasets and the practical application of clinical care in a real-world setting of taking care of patients with COVID during a public health emergency, when doing very pristine, randomized trials just wasn’t very practical."

In addition to these four areas, Gottlieb says other secular trends are also underway that will accelerate the adoption of RWE. For instance, as enthusiasm is growing on the vaccine and therapeutic side, the FDA is building out a substantial database of clinical data gleaned from electronic health records (EHRs). Comparing it to the Sentinel system as a transformative element in the agency’s post-market tools, Gottlieb believes this database also represents a paradigm change that will augment the use of RWE. "The profound change will be that because FDA is now making decisions on the basis of these kinds of datasets, they’re going to have to invest very heavily in building out rigorous methodology for how you make regulatory decisions using this information," said Gottlieb.

Creating a standard methodology for using RWE for regulatory purposes, he believes, will provide a more-level playing field in the broader marketplace among payers, product developers, regulators, and clinicians who all want to use this information for decision-making. "I think very rich literature will grow out of this on how to use these data in a reliable fashion," he stated.

A second secular trend supporting wider use of RWD is the widespread adoption of digital tools and the use of telehealth; many patients are now comfortable receiving healthcare in this manner and providers can deliver healthcare effectively with digital tools. "I think this is going to make it more practical to collect real-world evidence when you have more decentralized tools for collecting clinical data; the adoption curves will be permanent and continue to accelerate," he said.

Additionally, Health and Human Services (HHS) interoperability rules and regulations set up a secure standards-based API requirement to support patient access to their own electronic health information with third-party apps. This could have a large effect across the entire industry and, again, accelerate the adoption of RWE in regulatory and clinical decision-making, Gottlieb noted. While the near-term might be a "noisy environment" because numerous applications will come into the market at the same time, "I think it’s going to create a very dynamic environment where access will be the first step, if you will, toward doing something really important with this information that’s much more practical to the provision of care, and it’s going to be much more tangible to patients and providers," Gottlieb stated.

Having an open API with more-consistent standards across the healthcare spectrum will allow healthcare organizations of any size, even small ones, to more securely exchange information, he stated, noting, "That will open up more opportunities for patients to get that information, remove uncertainty around the standards, improve interoperability, obviously, and help healthcare organizations communicate data more easily with each other and with partner organizations."

This will help the exchange of information become more standardized and enable digital health vendors to connect with other systems more easily and exchange data more seamlessly. "It also comes with a lot of obligations to measure and protect patient privacy and security. I would expect to see additional rule-making and guidance around patient privacy issues because they have been raised so prominently, but I think that this really changes the market," said Gottlieb.

Gottlieb noted a final trend: "I think you’re going to see greater adoption by payers as well, which we’re already seeing. As these methodologies are used and proven out in a regulatory context, I think payers are going to use them more readily to inform decisions...There always was a need for better information to inform reimbursement decisions. Now we are developing ways to provide that information in terms of the consolidated datasets and the more reliable methodology."
Currently, RWE has been used in about 16% of all the cited clinical studies in specialty drug decisions by payers, with EHR data as the most often cited data sets being used to derive these insights. As FDA makes wider use of these data around drug decisions, Gottlieb believes payers will become even more comfortable relying on these same approaches for their coverage decisions. Overall, Gottlieb made clear that the adoption curve around the use of RWE has been accelerated, not just by the public health crisis that we’ve been facing, but also by several secular trends that were underway before the crisis and have continued to grow. He summed up by stating, “There’s a real significant opportunity that this is going to accelerate in the coming years, and we’re all going to have a better healthcare environment because of it.”

Data Collection and Need for Transparency

Following these opening remarks, Sy Pretorius, MD, led a lively discussion among the roundtable participants.

MARC BERGER, MD (CONSULTANT): I agree with Dr. Gottlieb that we already have excellent progress on methodologies for how to analyze these data. I think that the most important thing that’s going to come out of the FDA now starting to play with EHR data is they’re going to get first-hand use in using the data. They’ve been given a lot of recommendations about how they should be thinking about the use of these data, but they’ve been very cautious about applying it in regulatory decisions. I think that only with experience is the FDA going to be more comfortable with making those kinds of decisions.

GOTTLIEB: You’re spot on that the agency will have to accept and validate those methodologies for its own regulatory purposes. I think we can accelerate the adoption and sort of solidify the reliability of those approaches. Even if they were reliable before, I think the act of a regulatory agency putting out guidance documents around what the proper approaches are for making certain kinds of decisions based on information, as long as they do it in a thoughtful way, will create a sort of level playing field on what the proper approach is for answering a certain question.

SIMU THOMAS, PhD (ALEXION PHARMACEUTICALS): You mentioned that we will observe greater adoption of RWE by payers, once we standardize the benchmarks to make these data sufficiently robust to inform regulatory decision-making. This is critical. Payers have been open to using RWE for some time now to bridge knowledge gaps but have been waiting for the regulatory agencies to endorse frameworks for use of these data for clinical decisions. The key is for these multiple stakeholders to appreciate that RWE complements RCT findings, adding incremental perspectives that are vital to both medical practice and patient access determinations.

RIAD DIRANI, PhD (TEVA): For the past 20 plus years, most of the efforts in RWE have been focused on post-launch evidence generation. We primarily focused on payer needs, reimbursement, and so forth. The growth over the last five or six years seems to be around clinical development and discovery, particularly on identifying and quantifying unmet need and burden of disease, and unbranded RWE around clinical trial programs. It’s critical for the C-suite in pharma to understand what RWE offers, where it fits into overall strategy, what value it contributes, and invest in infrastructure accordingly.

RWE Use Cases

PRETORIUS: A few years ago, Parexel commissioned a study with the help of the Intelligence Unit at The Economist to explore the drivers of innovation and identify innovations in drug development that could significantly improve the drug development process in terms of the timelines or the program’s success. RWE, and real-world data, in particular, was one innovation that rose to the top in the study, which looked at a very large sample size of products and developments. Programs and trials where real-world data and RWE were incorporated had a 21% greater likelihood of getting approval, compared with studies that didn’t. So clearly, RWE had an impact. What are some of the trends you are seeing in terms of the use of RWE to date?

AMANDA BRUNO, PhD, MPH (BAYER): There’s a lot you can do with RWE that doesn’t contribute to a formal study or a project. We can use it internally for planning such as better understanding oncology market, which is moving so quickly that without real-world data, we sometimes don’t know what our population looks like. This represents a large change in early clinical development, from using real-world data from first-in-human studies onward to inform how we might set our stage gates for go/no-go decisions within our organization.

CHARLES MAKIN (BIOGEN): Yes, it’s been fascinating to be a part of this evolution in RWE over the past few years. We used to see RCTs informing RWE and now in many instances it has gone the other way around, where we have RWE informing RCTs. Newer areas that have witnessed a lot of growth in the past few years include clinical trial optimization, an area that didn’t use RWE until seven, eight years ago. We had been doing trials the same way for 80 years until the past decade when we started, for example, doing site identification and developing heat maps of practically real-time patient populations using real-world data. The creation of RWE and improvement in patient outcomes and clinical care go hand in hand. In some cases, RWD is shared in real time at the point of care by providers to enable them to deliver more tailored care to their patients. So, it’s a true personification of personalized medicine while generating data that can really lead to a lot of interesting insights from a RWE perspective.

BERGER: Real-world data are used extensively by the marketing and the sales side of organizations as well. So, understanding the patient journey, what subpopulations might benefit the most from a new innovation, treatment patterns, obstacles to adopting new technologies, obstacles to adherence and using it for monitoring ongoing comparative effectiveness once a product is on the market are all becoming standard practices at larger pharma companies. Real-world data has infused itself entirely across the entire value chain from discovery to optimizing clinical trial design and beyond.
ARIJIT GANCOLI, PhD (ASTELLAS): We always talk about RWE, but unless we have a strong infrastructure to collect the data and make it more purposeful, the evidence is all dependent on the quality of the raw data. So that’s one shift; institutions or pharma companies are investing in RWD in addition to thinking about where the RWE will lead.

At Astellas, the RWE studies are driven by the scientific functions. Another area for us is to understand how RWE collected from a region (say, the US) could be expanded to a global audience, which is a critical part in enhancing the value of RWE for external stakeholders.

DIRANI: To me the biggest growth over the last five years in RWE has really been around clinical development and discovery, as Marc mentioned. But what’s also new is that senior management and the C-suite executives are now focused on RWE and building internal capabilities and infrastructure around that. Over the last couple of years, my company has had tremendous growth in our internal capabilities to identify unmet medical needs, the value element, and the engagement with the commercial side.

GOTTLEIB: There’s another aspect of decision-making to discuss. When we look at what will happen in 2021, drug pricing legislation is inevitable, leading toward some kind of adoption of a plan where the industry ends up agreeing to some form of price regulation, if you will, in exchange, perhaps, for measures to try to expand consumer eligibility for and access to drugs. RWE can become very important, I think, in terms of driving discussions about pricing and how those assessments are made.

GREGG SYLVESTER, MD, MPH (SEQIRUS): My company is focused on influenza vaccines, and all vaccine manufacturers have an additional hurdle to bring a vaccine to the public. The Advisory Committee on Immunization Practices (ACIP) must recommend the use of a vaccine after the FDA licenses it in order for widespread use of a vaccine. The ACIP doesn’t automatically approve or recommend something just because the FDA has licensed it. But we have found that the World Health Organization (WHO)’s National Immunization Technical Advisory Groups (NITAGs) and our public health agencies have always accepted RWE. RWE doesn’t replace RCTs but augments them. There is no question that NITAGs are looking at RWE.

At Seqirus, we have set up a database that merges EHRs with claims data. This is important because health information comes from various sources in the US. As many as 50% of adults get their flu shots in pharmacies, where the information doesn’t necessarily link back to their EHR, but we capture those individuals in our database through our billing or claims dataset and link it to the HER data. This makes our RWE studies more robust.

Expansion of RWE with the Oncology and Rare Diseases Market

PRETORIUS: How might RWE affect the oncology and rare diseases market?

NUWAN KURUKULASURIYA, PhD (MORPHOSYS): A topic that has been neglected for far too long is clinical heterogeneity. If you look at oncology clinical trials for the past 20 years, what is apparent is that the study populations don’t fully reflect the complexity of the disease. Inclusion and exclusion criteria are very limiting. Patients with comorbidities are typically excluded. Ethnic minorities are not adequately represented. In fact, some studies suggest that only a fraction of the oncology population (low single digits) are truly reflected in randomized, controlled clinical trials. A recalibration is necessary and long overdue. RWE is the solution.

The promise of RWE is to better reflect clinical heterogeneity and bridge the so-called “efficacy-effectiveness divide” by complementing the traditional interventional clinical trial approach (demonstrating efficacy) with innovative, more expansive observational strategies (highlighting effectiveness). We will have to partner and build synergies across industry, academia, government, and nonprofit—and be committed to doing things differently in order to fully unlock the promise of RWE. Taking a multi-stakeholder approach will allow a better framing of the scientific questions we want to address and gain alignment on cutting-edge RWE methods and mechanisms we jointly deploy.

One of the most innovative RWE methods currently being explored is the use of “synthetic controls.” At MorphoSys, we have used such an approach to accelerate drug development and successfully gain FDA approval for a novel therapeutic-regimen in the immuno-oncology space, Tafasitamab plus Lenalidomide for relapsed-refractory transplant ineligible Diffuse Large B-Cell Lymphoma (DLBCL). In partnership with Paraxel and others, we were able to tap into large real-world data sets in order to create a “synthetic control” that was in-turn compared with an open-label treatment arm.

Ultimately, RWE better reflects the patient experience and will likely play a key role in shaping future oncology (and rare disease) clinical development programs and regulatory pathways.

We always talk about RWE, but unless we have a strong infrastructure to collect the data and make it more purposeful, the evidence is all dependent on the quality of the raw data.

CHRIS GARABEDIAN (XONTOGENY): The ultimate goal of most biotechs and pharma companies is to use data to get drugs approved. I think we need additional methods to capture and supplement these RWE data. Ideally, we want to capture everything discussed here plus biomarker data, patient outcomes, patient-reported outcomes, genetic testing, etc. The list will grow. Newer genetic technologies are focusing more on some disease areas and subpopulations that have never been tested before.

In rare disease specifically, unless you’re looking at spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) and a handful of other more well-studied targets, many of these are new areas where we haven’t even defined endpoints. We have to do natural history studies to even identify them.

If we can show that these new RWE data sets are actually more informative and concordant with traditional methods, acceptance will grow. Until then, I think there’s a lot of opportunity for these approaches to help get drugs approved by focusing on the totality...
of these data. That’s an important point on how we evolve this RWE.

**THOMAS:** RWE is vital in rare diseases. There are over 7,000 rare diseases, however approved treatments are available only for 5% of them. What happens in the remaining 95%? Patients have no treatment options or are treated with unproven therapies and physicians have to make decisions based on real-world experiences that are often rather sparsely documented. Ideally, we should develop clinically proven treatment options for each of these rare disease areas and RWE and experience should provide complementary, scientifically robust validation for proper management of these patients.

**AMY MCKEE, MD (PAREXEL):** I’m an ex-FDA regulator in the oncology space. One thing we have to keep in mind is that the FDA, as a public health institution, has safety as its primary goal. Yes, they may be conservative in how they come around to accepting some of this.

They take into account the regulatory risk, so we see that use of RWE is already in place in disease areas where the risk-benefit calculation is a little bit different. This includes rare diseases, oncology and other places where there is high unmet medical need. I think, we can push the envelope in terms of FDA acceptance, but we have to keep in mind that they see a regulatory risk, too.

**LEANNE LARSON (PAREXEL):** To tie together a couple of points—we’ve talked about how RWE and RCTs can inform each other. That feedback loop is really important. When we have these critical therapies coming through the clinical trial process, as we get to the end, as Nuwan was mentioning, we don’t see the clinical heterogeneity that we need to see in those populations in order to support broad decision-making. Being able to take those trials out into the real-world setting and better understand those patient subgroups—the realities of response, prescribing behaviors, patient behaviors and compliance, payer acceptance and payer needs—will be critical.

We’ve also talked about how the regulations are changing around the world and the importance of FDA in driving and setting the tone for a lot of the decisions. Now, we’re starting to see some evolution in those spaces with the NMPA in China issuing guidance and on the payer side, the health-economic side, NICE also issuing their guidance.

This needs to be a truly “learning” system and a model, where we’re informing each other and informing healthcare more effectively through being able to learn from all of the data and every patient.

**BILL TUBBS (VISTERRA):** I wonder if we need to push the limits on this. We develop products for kidney diseases, and we’re now developing a product for IGA nephropathy through the Accelerated Approval Program. We do have a surrogate endpoint. However, in things like kidney disease where kidney failure takes a long time to develop, are we at a stage where to demonstrate your product prevents kidney failure, it requires a 10- to 20-year study? It seems to me at that point, we’re outside the realm of randomized controlled trials and need to do some serious thinking about the power of real-world data and RWE to help us demonstrate a benefit for these long-term outcomes.

The issue I’m raising is time.

**BERGER:** The COVID situation has highlighted how much further we have to go in the US to develop a learning healthcare system. Britain was able to very quickly execute a large, simple trial and gain a lot of input and information very quickly. We’ve tried to build that kind of infrastructure in the US with the PCORnet, but it hasn’t been quite as successful. If we can get the infrastructure in place, we can lower the overall cost of executing clinical trials and deal with what is a rather broken system of Phase III trial execution in the US.

**CANGULU:** Another area to discuss is using more RWE to identify outcomes that are meaningful to patients. RWE has the strength to open up a window for these outcomes that may have never been considered in regulatory and reimbursement decision making.

**GOTTLIEB:** I think that adoption curve is already well underway and actually further along than the adoption curve in trying to use some of these constructs to answer regulatory questions around primary, secondary endpoints, things that are sort of harder measures in a clinical trial than you would typically use a randomized approach for.

I think on some of the data collection and some of the questions where randomization either isn’t necessary or isn’t practical, that’s where you see RWE really becoming more important and particularly around things like PROs and endpoints that try to glean the patient experience.

**MAKIN:** Circling back to the rare diseases piece, the evolution has been fascinating—when we are dealing with so many rare diseases, we are truly talking about precision medicine—and precision medicine requires precision data. And then we get into discussions about which is the best data source to address a specific research or business question (Do we need to collect clinical data or PROs? Can we use existing data from EMRs or claims etc.?). The thing to remember is that real-world data is a continuum of evidence; the specific type might not matter as long as it’s fit for purpose, has scientific integrity, and provides the answers we need.

**CARABEDIAN:** I think we can be informed by the rare disease experience for more prevalent diseases. If we can get better population statistics around some of these diseases, much like natural history is used in rare disease, then we can start to make an argument to the FDA and make it easier for them to acknowledge that you’ve shown your drug’s benefit, moving toward some of these more longitudinal or non-placebo-controlled RCTs.

**PHERBER:** Let’s pivot toward forward-looking statements. Where is RWE going to go in the future?

**MARK DE ROSCH, PhD (EPIZYME):** We just got our first product approved for epithelioid sarcoma and follicular lymphoma using the FDA’s Accelerated Approval Pathway. Right now, the primary area we’ve been looking at for RWD is on synthetic controls, where we’re using single-arm studies to get accelerated approval.
pathways with surrogate endpoints. In rare diseases, it’s very difficult to do RCTs because there are so few patients. For example, only 100–120 epithelioid sarcoma cases are diagnosed each year. The concern, though, is that with all these data (from EHRs, digital sources, and wearables), how do we separate the wheat from the chaff in all of those data and the methodologies for internal decision-making, and resource allocations, and regulatory decision-making?

MATS ROSEN LUND, PhD (DAIICHI SANKYO): I share those concerns, and have a closing question regarding the role of the regulators and how the FDA looks into the future. The FDA and Brigham and Women’s Hospital have expanded their previous RCT DUPLICATE, which is a RWE project. As part of the project, researchers will, for the first time, estimate the results of randomized control trials that have not yet concluded. In funding the project, Congress wanted the researchers to think hard, not just about how to use this information for post-market safety surveillance, but also for post-market evaluation of efficacy. This should significantly increase the use of RWE.

Summary

Gottlieb closed out the discussion by noting the RCT Duplicate project represents a clear directive for the agency to use RWE in regulatory decision-making. “Congress wanted the agency to think hard, not just about how to use this information for ‘postmarket safety surveillance,’ but also for premarket evaluation of efficacy,” he stated, again noting that there’s a real cultural commitment to RWE at the agency and it will accelerate the adoption and the use of this information in clinical trials, clinical development, and for regulatory decision-making.

COVID-19 has further accelerated this adoption and has spurred a discussion in the United States for deep thinking about how to create a better clinical data-collection infrastructure that is pandemic-ready and that can be used to help answer important questions in the setting of a public health crisis. In addition, he predicts we’re going to see the data architecture change very quickly in the coming years owing to these trends and others. He stated, “I think we’re going to see those become much more mainstream going forward in a very positive way for patients.”

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