SPOTLIGHT ON: REAL-WORLD EVIDENCE

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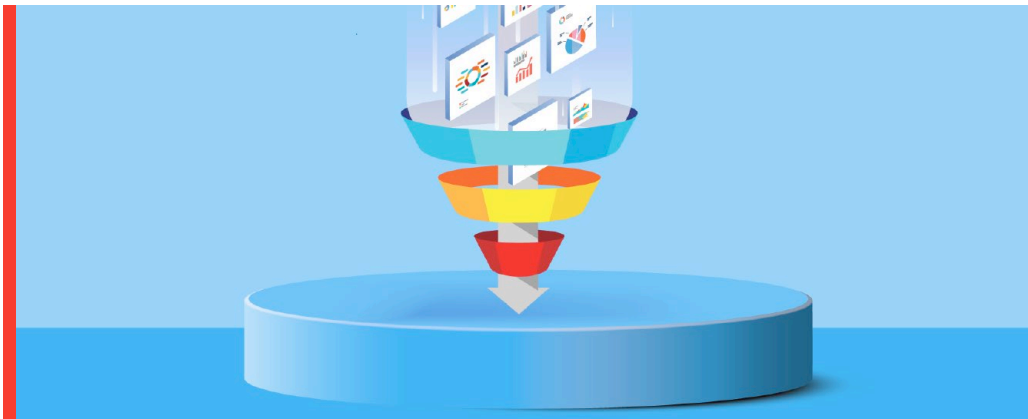


Bringing down real-world evidence barriers in China

Survey by BioCentury and Happy Life Technologies finds high hopes but delayed expectations for RWE to deliver value in China R&D

A role for RWE in the accelerated approval pathway

Real-world evidence is poised to make its mark on confirmatory trials

Aligning on the advancement of real-world evidence

RWE Alliance members aim to provide a united voice on how regulators can deploy real-world evidence in decision-making

The pivotal role of real-world data in a pandemic

Drug development for COVID-19 will depend on real-world data and industry is stepping up to implement it

BIOCENTURY

PRODUCT DEVELOPMENT | REPRINT FROM NOV. 10, 2021

Bringing down real-world evidence barriers in China

BY LAUREN MARTZ, SENIOR EDITOR AND RIMMEL SHEKHA, BIOPHARMA ANALYST

Real-world evidence is working its way into global clinical development and commercialization strategies with an impact that's expected to grow, but implementation is lagging in China.

Recent policy changes to promote use of RWE in drug development in China could mean a surge in adoption is on the horizon, once awareness rises and other barriers to implementation come down.

Strict data privacy laws, data integrity concerns and a lack of institutional experience with RWE studies are among the biggest perceived barriers to RWE uptake in China, according to a survey conducted by BioCentury and Happy Life Technologies (HLT) Group (Figure 1).

The survey results also conclude that though some companies are using RWE for post-market assessments, there's opportunity to add value in pre-market clinical development applications, and in reimbursement negotiations both in China and globally.

The survey of more than 80 biopharma executives, professional service providers, investors, and government and non-profit groups was conducted via live polling from Oct. 6-25.

Historically, RWE has been an important type of evidence for monitoring vaccine and therapeutic safety after approval. With the growing body of electronic medical data, tools to analyze the data and innovation in clinical trial design, more applications are emerging.

The pandemic represented a turning point for RWE, drawing industry attention to its potential to supplement standard clinical trial data, and accelerating its adoption. Alternative clinical development tools capable of speeding evidence generation and capturing effects across diverse demographic groups became important as traditional clinical trials became more difficult to execute.

RWE also emerged as a valuable tool for tracking outcomes after authorization of medical countermeasures that had been rapidly developed.

The applications are now clear, but a set of internal and external barriers has created hesitancy among both companies and regulators. The survey results suggest those barriers are being dismantled, and that the reach of RWE should start to extend past the post-market monitoring applications where it has a solid footing to begin making more contributions to trial designs, regulatory decisions and payer negotiations.

Global optimism for RWE

Executives surveyed by BioCentury and HLT agreed the momentum for RWE generated during the pandemic is likely continue building in the coming years.

Of the 81 participants surveyed, 91% envision the use of RWE changing over the next five years, with nearly half expecting a large increase in adoption of RWE by companies and acceptance by regulators.

Buy-in from companies and regulators may need to go hand-in-hand because companies aren't motivated to perform the studies without a reasonable expectation they'll be accepted by regulators, and regulators can't have confidence in RWE studies without research from companies to validate them.

Of the two disease areas where respondents expect RWE to make its biggest mark, cancer and rare diseases (Figure 3), the latter may stand to benefit more from incorporation of RWE in the development pathway.

Due to scarcity of patients, using real-world data to guide site selection, stratify patients, and substitute for placebo control arms is particularly valuable in rare diseases.

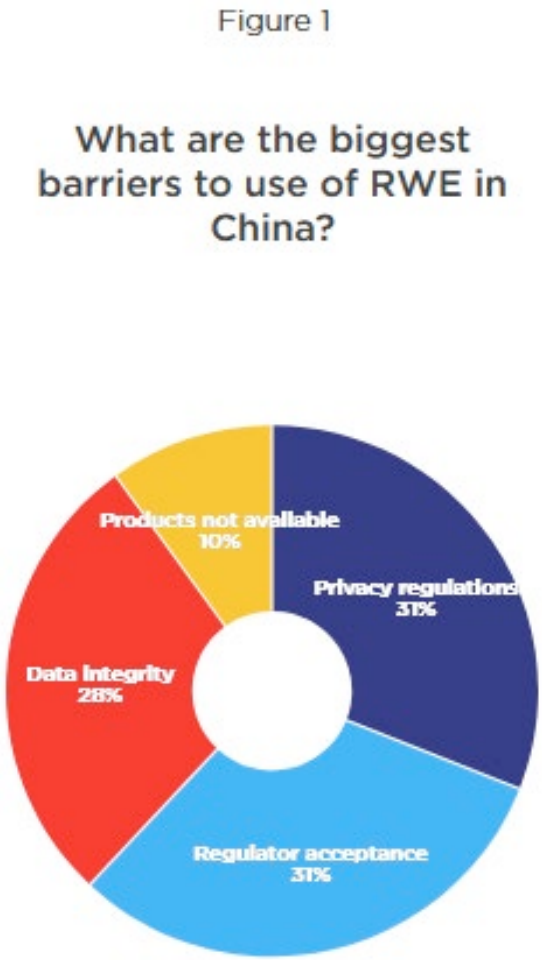
Meeting clinical endpoints in a cost-effective way can be challenging for many rare diseases, suggesting development could be incentivized by use of RWE as a postmarket tool to confirm benefit after approvals, based on limited or surrogate data.

Across disease areas, RWE has already penetrated postmarket settings, and survey respondents believe that is still where these data are likely to be most effectively used in the next five years.

While safety assessments are a validated application of RWE, survey participants are most excited about the use case of postmarket efficacy assessment (Figure 4).

With the expanding use of accelerated approval pathways to help drugs reach patients faster, there's an increased need for post-market research tools such as RWE to provide a complete picture of clinical efficacy and safety. This year's BioCentury Back to School collection calls for greater use of RWE in confirmatory trials for accelerated approval.

Figure 1



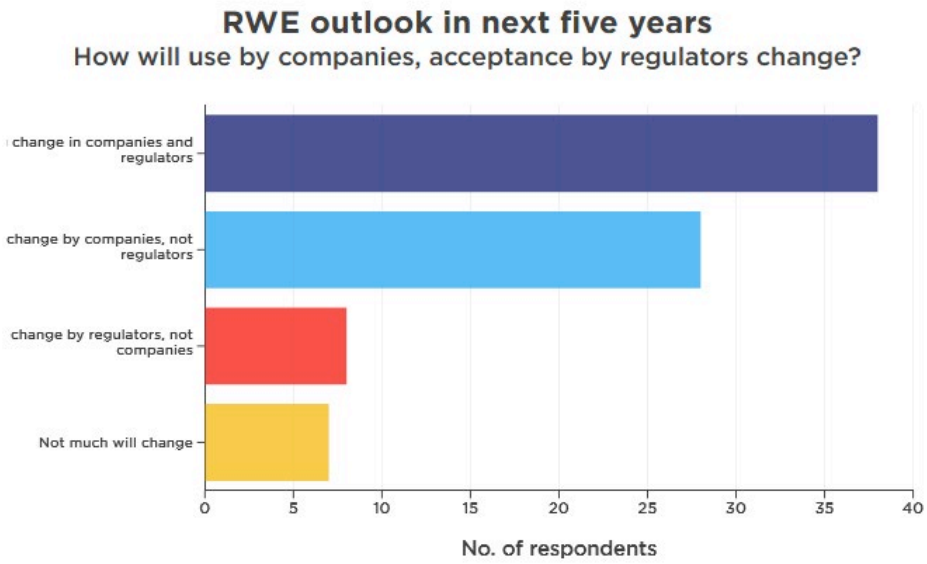
Bringing RWE to China

Real-world evidence was once perceived as off-limits in China due to privacy, data and regulatory barriers, but policy has recently started to change to enable broader use of RWE, particularly by Western companies bringing therapies to China.

Several guidelines covering the use of RWE in clinical development have been released in China since the beginning of last year.

Use of RWE is also now encouraged in Hainan Province's Bo'ao Lecheng International Medical Pilot Zone, where drugs approved in the U.S., Europe or Japan, but not yet in China, can be deployed by physicians and RWD in Chinese patients can be generated. Several products have been approved by China's NMPA based on RWE generated in the pilot zone.

Figure 2



Despite the warming regulatory environment, growth in use of RWE remains slow, in part because of a lack of awareness.

According to the BioCentury/HLT survey results, most industry representatives aren't aware of Hainan's Pilot Zone.

The survey captured responses from 39 people in North America, 34 in Europe and 6 in Asia. Overall, 34 (43%) of the respondents said they have business in China.

Less than one-third of those who answered the question (19/62) said they were aware of free trade zones that allow use of RWE in regulatory submissions to NMPA, and the use of therapeutics and devices approved in other regions (Figure 5). However, 44% (26/59) expect the free trade zones have a high or very high likelihood of driving future use of RWE in China (Figure 6).

Among the companies that said they do business in China, less than one-third said they've used RWE in the country; however, another third are considering it (Figure 7).

The most common applications for RWE in China are related to marketing and commercialization, according to survey responses (Figure 8). These are the low-hanging fruit for RWD implementation, but the results also suggest the number of companies using RWE in China may be overrepresented by the survey. Some companies consider market research such as surveys to be RWE, but that doesn't fall under BioCentury's definition of evidence generated from data collected in claims databases and electronic medical records.

Emerging opportunities for RWE include clinical research and reimbursement negotiations, both of which are being pursued by some companies in China. In clinical trials, RWE can feed into trial design by identifying the best trial sites based on patient concentrations and providing information about disease prevalence and natural history. It can also serve as historical control arms to avoid unnecessary placebo administrations.

In payer negotiations, RWE can provide a broader picture of safety, efficacy and durability in clinically relevant populations than can be captured in standard randomized controlled trials.

Remaining barriers

Despite the growing regulatory acceptance in China, companies globally still see data privacy, integrity and regulatory acceptance as problems in the region (Figure 9).

Data integrity issues extend beyond China to the global state of data quality and standardization. One problem with data for RWE, which usually comes from electronic medical records and insurance claims databases, is that the data aren't necessarily structured for research purposes.

Data can be incomplete, not digitized, and not standardized in scales, collection or recording methods.

China's later entry to RWE generation gives it an opportunity to build an infrastructure that's standardized and allows companies to extract data relevant to drug development from the start.

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Figure 3

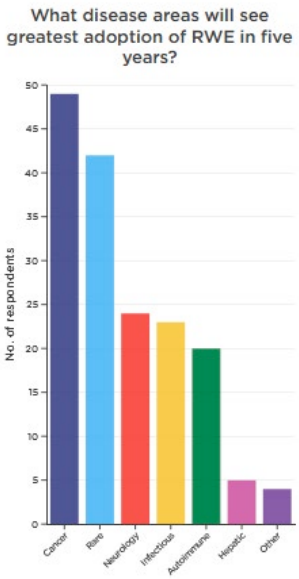

Figure 4

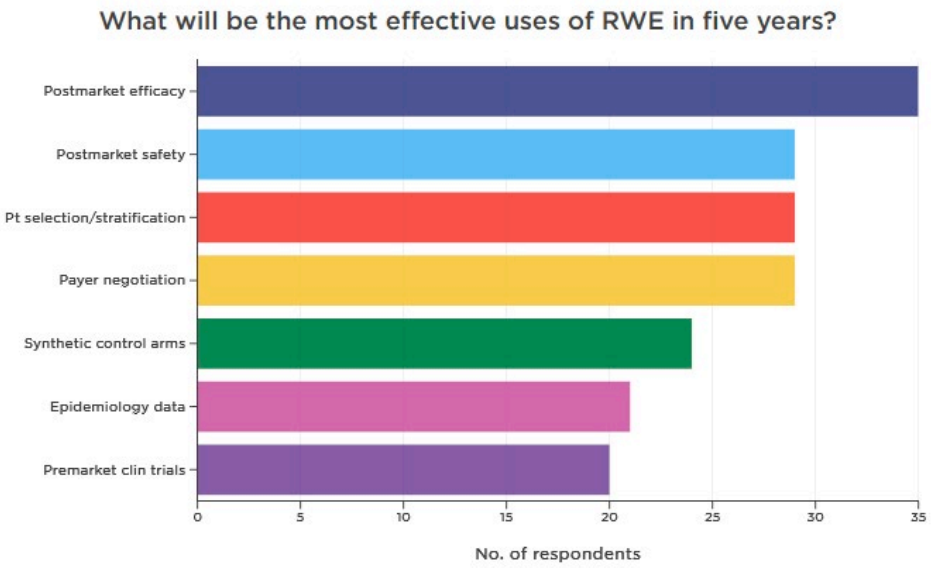

Figure 5

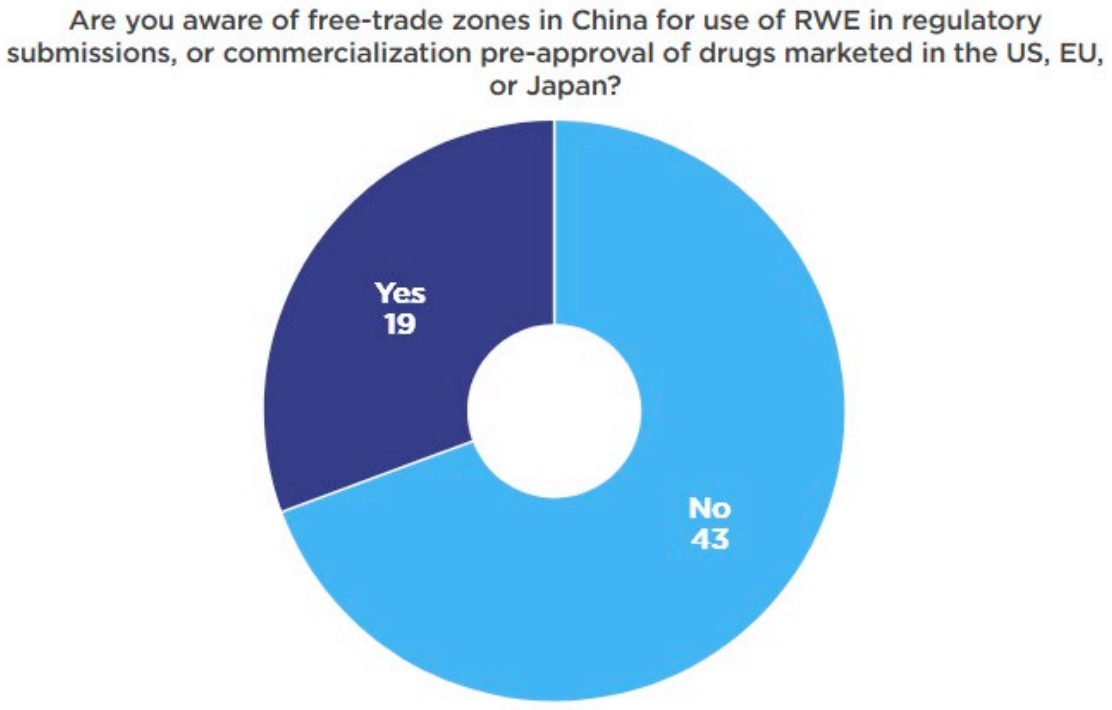

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Figure 6

How big an impact will these free-trade zones have on western biopharmas conducting RWE studies in China?

Figure 7

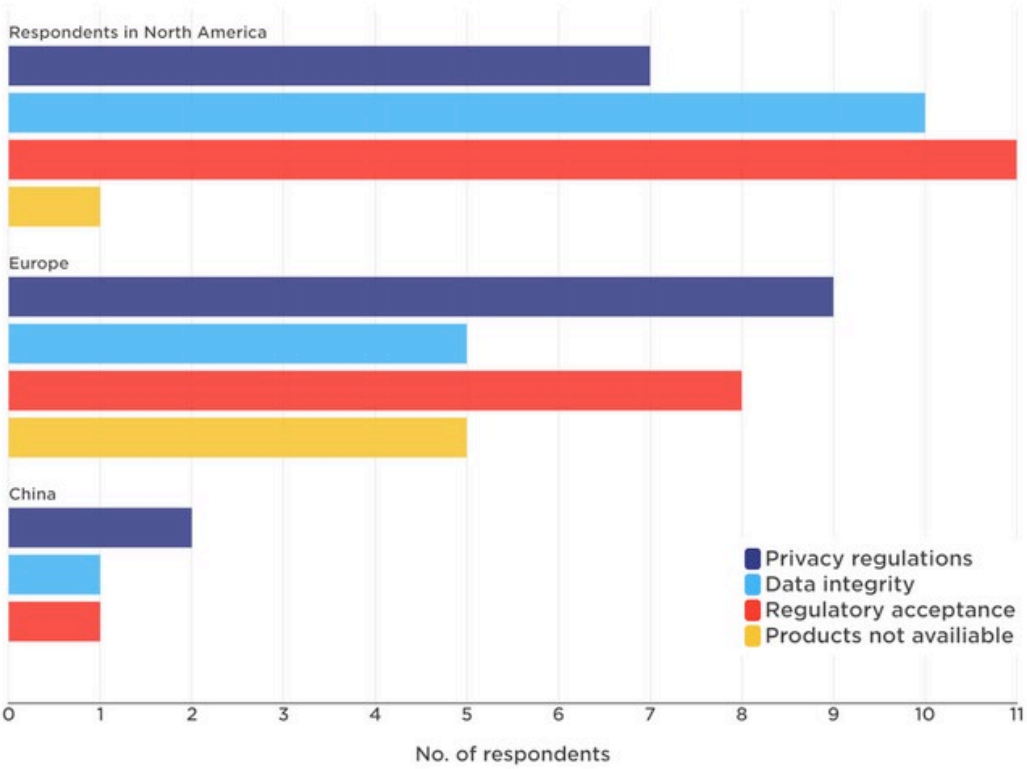
If doing business in China, have you used RWE sources from China?

10 YES

11 NO,
UNDER CONSIDERATION

13 NO,
NOT UNDER CONSIDERATION

Regional views of RWE barriers in China



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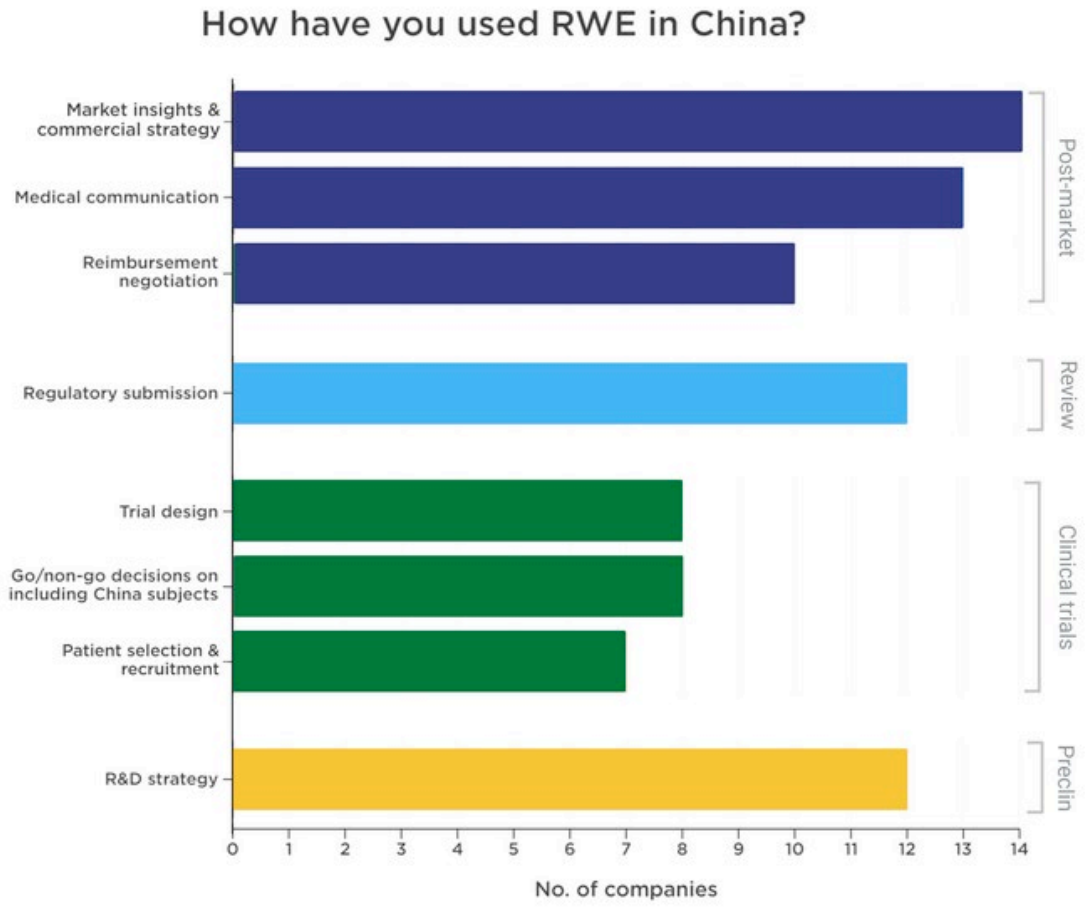

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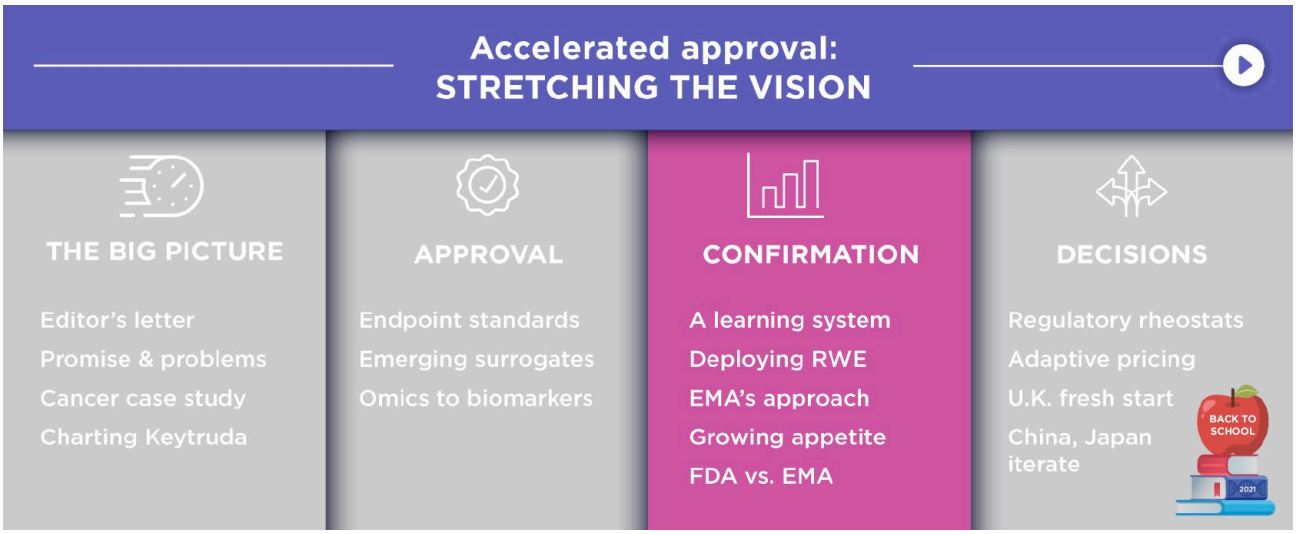
A role for RWE in the accelerated approval pathway

BY LAUREN MARTZ, SENIOR EDITOR



Real-world evidence is still in its infancy, but as its potential becomes increasingly recognized, doors are opening that could render it a difference-maker in the accelerated approval pathway.

In particular, RWE could be key for opening up accelerated approval to more diseases and making confirmatory trials more informative.

RWE is inching its way into clinical development, gaining footing in postmarket safety monitoring and, occasionally, in trials that deploy synthetic control arms. It's rarely, if ever, been used as a tool in confirmatory trials for drugs that receive accelerated approval.

According to stakeholders interviewed by BioCentury, that's going to change.

Ongoing improvements in systems for gathering and deploying RWE will parlay into benefits for the confirmatory trial phase of accelerated approval, providing a broader picture of safety, efficacy and patient access across racial, geographic and socioeconomic groups than is possible with the single clinical study typically used to meet the confirmatory requirements.

This type of data can help pinpoint the subpopulations who benefit most from a drug and build confidence that clinical benefits will hold up outside clinical trial frameworks. It would complement biomarker analyses in refining patient groups.

Moreover, for some rare diseases, RWE may be the only practical avenue for confirming benefit.

RWE is still budding as a tool in clinical development, however, and the process of data collection and analysis has yet to be refined and efficiently integrated into the clinical development framework. Still, stakeholders who spoke to BioCentury believe certain RWE study designs — pragmatic trials in particular — may become useful in the confirmatory trial setting in the near term, and could sidestep many of the traditional challenges associated with RWE studies.

Converging on RWE

EMA is also committing to broader use of RWE in the regulatory process. In the 2021-23 work plan for the joint

HMA/EMA Big Data Steering Group, the agency outlined plans to establish a network for collecting and analyzing RWE through the Data Analysis and Real World Interrogation Network (DARWIN-EU). It aims to deliver routine access to RWE for regulatory decisions by January 2023.

A draft of the pending 21st Century Cures Act 2.0 in the U.S. lays the groundwork. It specifies that RWE could be used to fulfill postmarket requirements for drugs that receive accelerated approval to demonstrate clinical benefit.

The expanded use of RWE during the COVID-19 pandemic is also helping to establish it as a regulatory decision-making tool.

"We're seeing FDA expand its use cases for real-world evidence, and that dovetails with its more aggressive use of the accelerated approval pathway. Everything is ripe for this to happen," said David Thompson, SVP of real-world research at Syneos Health Inc., which provides both CRO and CCO services.

"After so much of industry's pipeline was diminished during 2020, FDA has committed to not lowering standards, but to bringing together alternative approaches including RWE generation to complement existing approaches," said Jeff Elton, CEO of ConcertAI, which supports clinical development and commercialization through the use of RWE and AI.

In the near term, RWE is likely to serve as a complement rather than a replacement to randomized-controlled confirmatory trials, and should help both refine the appropriate patient populations and generate initial confirmatory data quickly.

RWE offers a chance to stratify patients based on clinical features captured in routine care. By including larger, more diverse study populations than traditional randomized-controlled trials, RWE studies can pick up more diverse safety and efficacy signals and allow researchers to assess whether those signals correlate with any of the patients' clinical or demographic features.

The use of RWE studies is unlikely to change the clinical outcome measures that are required to convert an accelerated approval to final approval. But RWE can start reducing the uncertainty around benefit sooner because the studies begin generating data quickly and can be analyzed on a rolling basis as data accrue. Moreover, if the confirmatory trial result turns out to be ambiguous, RWE could be key to increasing confidence in the efficacy finding.

"As soon as a product is on the market, you can start collecting real-world data related to its use and analyzing real-world data to generate real-world evidence," Thompson told BioCentury.

Said Elton, "Real-world evidence allows for much larger study sizes and allows you to pull out data for interim analyses at any point."

Another benefit, said Irene Nunes, is the long-term follow-up that RWE studies enable. "RWE can be generated from longitudinal data collected at the point of care, which is extraordinarily important for evaluating a drug or device in the clinical setting." Nunes is VP and head of regulatory affairs at the Flatiron Health unit of Roche (SIX:ROG; OTCQX:RHHBY).

While participants can drop out of clinical trials, and long-term patient follow-up is expensive, longitudinal patient tracking is easier in the real-world setting through registries and health records. Longitudinal data become more important the farther away the clinical outcome goalpost, which is the case for slowly progressing diseases and new modalities such as gene therapies where durability and long-term safety are uncertain.

Getting pragmatic

Different RWE study structures provide different types of evidence. While prospective and retrospective studies both will have a role in the postmarket setting, prospective pragmatic trials may prove most useful.

Pragmatic trials function as the RWE equivalent of a traditional randomized-controlled trial, selecting patients and study criteria up front, but operating within standard clinical practice with fewer eligibility restrictions and protocol requirements.

The benefit of prospective trials in confirmatory studies is that they're interventional, giving regulators and sponsors control over the patients included and the data points recorded. That ensures the right data are collected to answer the specific questions of the confirmatory phase, while minimizing the data collection and interpretation issues that arise with retrospective RWE studies.

They're also randomized, which means they don't suffer the interpretability issues of non-randomized retrospective studies.

The biggest challenges with retrospective studies, which involve scraping and analyzing past data from electronic medical records or claims databases, is ensuring the integrity of the data and that it's fit for purpose.

There's hesitancy in adopting the newer clinical trial design because many companies don't have the same kind of experience with RWE studies as traditional studies, and few health systems have the capabilities to embed trial protocols to

enable controlled data collection into routine clinical practice and electronic health records.

Thompson believes pragmatic trials will become an increasingly important part of postmarket follow-up as they become more embedded in routine clinical practice and electronic health records.

Drug or disease registries can complement pragmatic trials and other types of RWE studies. In rare diseases, registries could be especially useful for characterizing outcomes because the small patient populations make traditional trials challenging, if not impossible, due to the inability to enroll enough patients to statistically power the study.

Registries that can characterize outcomes with sufficient rigor to satisfy commitments to confirm clinical benefit will put accelerated approval in reach for more many rare diseases.

RWE also has a role to play earlier in the expedited approval pathways. The heavy reliance of regulators on single-arm studies as the basis of expedited approvals could make historical control arms sourced from real-world data an increasingly important tool.

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PRODUCT DEVELOPMENT | REPRINT FROM MAY 28, 2021

Aligning on the advancement of real-world evidence

BY STEPHEN HANSEN, ASSOCIATE EDITOR

As FDA prepares to put a stake in the ground for how real-world evidence can be used in regulatory decision-making, executives from leading real-world data and analytics companies have highlighted the need for industry-wide standardization on the use of RWD and pointed to near-term opportunities for making real-world evidence a routine part of the drug development and approval process.

Last week, five of the most prominent companies working in real-world evidence (RWE) — Aetion Inc., the Flatiron Health Inc. subsidiary of Roche (SIX:ROG; OTCQX:RHHBY), IQVia Holdings Inc. (NYSE:IQV), Syapse Inc. and Tempus Labs Inc. — launched the RWE Alliance to advance the use of RWE, just a few months before FDA is expected to publish new guidance on how RWE can be used to support regulatory decision-making.

FDA's latest push into RWE is rooted in the 21st Century Cures Act, which established FDA's RWE Program, the framework for which was published in 2018, to evaluate the use of real-world data (RWD) to generate RWE to support the approval of new indications for already approved drugs, or to satisfy post-approval safety requirements.

The use of RWE is already commonplace in certain parts of the sector.

For example, pharmacovigilance has long used claims or health record data to pinpoint any postmarket safety issues, and RWE has become an increasingly useful tool in identifying and characterizing new biomarkers when outcomes data are longitudinally paired with molecular profiling data, largely in the targeted oncology space.

And some sponsors are already using RWE as the primary evidence to support a label expansion. One such example is the approval of an sNDA for Ibrance palbociclib from Pfizer Inc. (NYSE:PFE) to treat men with ER-positive, HER2-negative breast cancer, which used RWD from the IQVia insurance database, Flatiron's Breast Cancer database and the pharma's own safety database to support the safety and efficacy of Ibrance's use in the population.

RWE Alliance members highlighted cardiovascular outcomes studies (CVOTs) and external control arms as near-term opportunities where RWE can be more routinely deployed, and their hope is that increased communications between industry and regulators can help advance one of the most foundational aspects for any future use of RWE: a clear set of standards for data capture, aggregation and interpretation.

"There are specific goals we have that relate to creating global standards to transform data into evidence, and to help the entire industry start to put stakes in the ground about how and when to do that, and what those evidentiary bars are for doing this in a credible way," Aetion CEO Carolyn Magill told BioCentury.

Low hanging real-world fruit

Magill pointed to CVOTs as a potential starting point for using RWE in place of large, randomized trials, given that components of the often-used MACE endpoint for CVOTs are easily captured in electronic health records.

"Safety studies like CVOTs that use an active comparator are likely the lowest hanging fruit," she said. "With CVOTs, we capture the endpoints in claims and we do that routinely."

Aetion is working with FDA as part of a collaboration with Brigham and Women's Hospital at Harvard Medical School on a demonstration project call RCT-DUPLICATE to use RWE to predict the outcome of CVOTs.

Efficiency gains from the approach could be large. The RCT-DUPLICATE group conducted a pilot to see if it could predict the outcome of the Phase III CAROLINA trial, a CVOT for diabetes drug Tradjenta linagliptin from Boehringer Ingelheim GmbH.

"You can imagine how costly and comprehensive that effort was, and researchers were able to demonstrate nearly perfect concordance with our platform," Magill said. The outcome for the CAROLINA study was a hazard ratio of 0.98, while the RWE-predicted hazard ratio was 0.91, both of which would have resulted in the same regulatory outcome.

CVOTs often cost well over $100 million to conduct. The CAROLINA trial took nearly eight years to complete, enrolled over 6,000 patients across 43 countries and over 600 sites with a median duration of follow-up of over six years.

In contrast, Magill said it took only four months to conduct the RWE safety study of Tradjenta at a fraction of the cost.

"That's an example where we are capturing those data and we think there can be some stakes in the ground relative to how to approach this in a way that will be acceptable to regulators and clinicians alike," she said.

Of course it isn't always that easy. Last year, Aetion and the RCT-DUPLICATE group published the findings from their first 10 RWE studies designed to emulate CVOTs. And while encouraging, the data also highlighted areas that will require more work before RWE can be routinely used in a regulatory context.

The published data showed that nine out of the 10 RWE studies produced results that were not significantly different from the RCT data, with eight of the nine achieving "estimate agreement," meaning the results fell within the 95% confidence interval of the RCT results.

But just six of the 10 RWE studies achieved "regulatory agreement," meaning the RWE results would have led to the same regulatory decision as achieved by the RCT data. Three of the four trials that missed on regulatory agreement were placebo-controlled trials.

"These findings confirmed what we've long known in the RWE community — that it's a challenge to use RWE to emulate placebo-controlled trials, as there is no equivalent to placebo in real-world practice and therefore placebos are not observable in real-world data," Magill said. "The difficulty arises in choosing a real-world treatment to stand in the place of the placebo, and the initiative's preliminary findings shed useful light on how to refine that choice."

The studies showed, for example, that the selection of a DPP-4 inhibitor as a stand-in for placebo replicated the outcomes of placebo in the actual CVOTs better than sulfonylureas.

RCT-DUPLICATE is planning to emulate 37 RCTs in total, so further refinement could improve the outcomes going forward.

External control arms and other opportunities

The other low-hanging fruit for RWE could come in the form of external control arms and the ability to address payer or sponsor questions about the real unmet need in a given indication.

External control arms can benefit single-arm studies by providing a comparator where there normally isn't one, and they can make controlled trials smaller and cheaper by reducing the number of patients who need to be randomized to control.

"I think real-world control arms are going to be much more commonplace," Syapse CEO Ken Tarkoff told BioCentury. "There's tremendous opportunity to use real-world data to look at controls."

Magill agreed. "Not only is there opportunity, there is some urgency and necessity to use external control arms, especially for rare diseases or oncology. These are populations where time is of the essence," she said.

But as evidenced by the experience in emulating CVOTs, external control arms are likely best placed for situations where the control arm includes an active comparator, or for rare diseases where there is no approved therapy and so RWD would consist of best available care.

Flatiron CMO Mike Vasconcelles noted that methodological issues remained, including how to control for "unmeasured confounding variables" and ensure the external control arm cohort is a comparable population to the active trial cohort. "That might sound relatively straightforward, but it is not," he said.

Tarkoff suggested that RWE is one of the best ways for stakeholders to identify what the real unmet need is in a patient population. "The lowest hanging fruit is just trying to discover the unmet need," he said. "There are so many times when questions are asked about what is happening today, what is the unmet need? And real-world evidence is the most efficient and transparent way to answer that question."

Both Vasconcelles and Elaine Katrivanos, senior director of regulatory affairs at Tempus, noted that RWE could immediately provide a better understanding of how a given intervention performs in populations that are commonly underrepresented in clinical trials.

Katrivanos noted that clinical trial populations "may not always be representative of the broader, real-life population that's expected to take advantage of a given therapy. I think this is where RWE can help color in the rest of that picture," she said.

Guidance expectations

The executives hope that coming FDA guidance on RWE will be a milestone in moving industry forward in the use of RWE, with a large focus on standardization.

Each pointed to increased transparency or communication on standardization around data and use cases as an important opportunity for FDA.

"Probably the biggest thing we need to have happen is to have more regular dialogue between industry and FDA," Tarkoff said.

He said part of that increased communication should be focused on standardizing the terminology used when communicating with regulators about RWE. "Getting to a more common definition of things: what is real-world data? What is real-world evidence? What are the rules of the road for how it can be used by different stakeholders, how the FDA interacts with them, gives them confidence about what is quality real-world data and evidence?"

"How you accelerate the known benefit we all believe real-world evidence is, is to have common methodologies and then work to optimize the adoption of those methodologies," he added. "We all want the FDA to be more vocal about what studies and approvals are, or are not, working and then continue to engage with industry to understand — almost a cyclical process of refining what is regulatory-grade RWE."

Vasconcelles noted that the technology and infrastructure is sufficiently advanced for RWE that industry now needs to work with regulators to establish standards on how to best deploy RWE resources. "The foundation has been established," he said. "Now it's all about moving forward with building on that foundation in a way to find the right opportunities for that evidence in a variety of use cases and in a regulatory context."

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EMERGING COMPANY PROFILE | REPRINT FROM MAY 29, 2020

The pivotal role of real-world data in a pandemic

BY LAUREN MARTZ, SENIOR EDITOR

Real-world data is taking on a critical role in the age of COVID-19 drug development, where hasty authorizations are being made on limited datasets and natural history data is being collected in real time.

Teams across the industry have stepped up to adapt their data analysis tools to the crisis with the goal of applying previous learnings to benefit future patients. The challenge now will be scaling their systems to manage the unprecedented volume of patient data, while keeping pace with the evolving pandemic.

Before the pandemic, real-world data (RWD) had been gaining momentum as a tool to create a broader picture of drug safety and efficacy post-market, and to get drugs to market faster under accelerated and conditional approval pathways.

In the context of COVID-19, RWD can help guide clinical trial design and clinical practice, and assist in regulatory decisions.

RWD from COVID-19 patients have already begun to inform adjustments to clinical trial designs, endpoints and patient populations, and to informally guide clinical practice.

However, industry has been slower to act on RWD that could guide regulatory decisions.

FDA has authorized two COVID-19 therapies under accelerated pathways that rely on RWD to keep patients safe and get them the most effective treatments, but both have raised questions around safety, efficacy and proper patient subgroups.

Evidence from randomized and observational clinical studies is mounting against the controversial drug hydroxychloroquine, authorized on anecdotal evidence alone, but it hasn't been enough to drive FDA to rescind the authorization (see "Hydroxychloroquine Testing Hahn's, FDA's Independence").

And although the antiviral remdesivir from Gilead Sciences Inc. (NASDAQ:GILD) was authorized on randomized controlled data, there isn't enough trial data to determine which patients benefit from the drug, which is already in limited supply (see "Remdesivir's Challenge").

Those questions can be addressed by RWD, but with the growing demand comes a growing list of challenges. For COVID-19, there's a volume of patient data that analysts haven't seen before, and that needs to be turned into actionable information faster than ever.

Data are also being gathered from diverse sources, further complicating collection and analysis.

The industry groups turning to RWD believe the technological progress that's been made, plus the unprecedented willingness to share data during the pandemic, are creating the perfect conditions to incorporate the tools into clinical practice and regulatory decision making.

Feeding RWD into clinical trial design

The COVID R&D consortium, a collection of biopharma R&D leaders, identified RWD as a priority early on in the pandemic, and it is directing its activities to an area where the data are already starting to make an impact: clinical trial design.

That application is directly in line with the consortium's overarching goal of accelerating drug development (see "COVID R&D").

"We're learning about this disease as we're designing the trials. There was very little prior information, very little published data and certainly no clinical trials to replicate," said Anne Heatherington, SVP and head of the Data Sciences Institute at Takeda Pharmaceutical Co. Ltd. (Tokyo:4502; NYSE:TAK). She also leads COVID R&D's data sharing component. "What we're learning from real-world data is feeding into not just clinical practice but how we're designing clinical trials and picking which drugs to use."

The at least 15 biopharmas in the group are sharing clinical trial and patient-level RWD.

Its real-world data work, headed by Kathleen Gondek, VP of global health economics outcomes research and epidemiology at Takeda, and Heatherington's data science component are brought together to collect and interpret the RWD.

"We recognized quickly that data sharing is a really important piece, and we have to involve real-world data because there wasn't anything else. I think this is the first time in history that we've been in this place," said Gondek.

"WHAT WE'RE LEARNING FROM REAL-WORLD DATA IS FEEDING INTO NOT JUST CLINICAL PRACTICE BUT HOW WE'RE DESIGNING CLINICAL TRIALS."

ANNE HEATHERINGTON, TAKEDA

For clinical trial design, using real-world data to understand the natural history of the disease is critical, said Gondek, who noted that the growing body of COVID-19's natural history has been leading to changes in trial endpoints, inclusion criteria and therapeutic selection since clinical trials started rolling out. For example, Gondek noted that many trials pivoted to shortened, 14-day endpoints after learning more about the disease course and understanding that 28 days was too long.

"Only through having patient level real-world data will we learn what the relevant outcome measures are, what time point assessments are meaningful, and which patient populations to enrich," she added.

Within the consortium, real-world evidence has led to discussions around trial populations and potential concomitant medication use. The consortium is now using it to determine timing for trials and to ensure trial design and adaptation are aligned with analysis output.

COVID R&D is organizing a master protocol trial to initially evaluate repurposed therapeutics, but it hasn't disclosed details.

Jeremy Rassen, co-founder, CEO and chairman of healthcare technology company Aetion Inc., added, "I think the data can really help us understand the natural history of the disease, how it affects different groups such as older patients and those with kidney or cardiovascular disease, and that in turn becomes really important when thinking about who to include in clinical trials."

Building on past success

While RWD hasn't yet become the go-to tool for validating safety and efficacy of authorized therapies, the Reagan-Udall Foundation for FDA and Friends of Cancer Research are heading up an initiative -- dubbed the COVID-19 Evidence Accelerator -- to help guide FDA decisions.

And in May, FDA signed a deal with Aetion to generate information from RWD that will guide FDA decision making. Aetion gathers data from a variety of different sources, then uses analysis tools to interpret the information, but the company hasn't disclosed exactly how the real-world evidence it generates will assist FDA.

"The collaboration is just kicking off, so while we can't speak to study specifics yet, we anticipate the early work will focus on supporting FDA's understanding of the disease and its impact, including characterizing COVID-19 patients, measuring medication use among patients with COVID-19, measuring diagnostic use and identifying risk factors for COVID-19-related complications such as hospitalizations, ventilation and intubation," said an Aetion spokesperson.

A combination of technical advances made before the pandemic and data sharing during the crisis is creating the right conditions to accelerate the incorporation of RWD into regulatory actions and clinical practice, even beyond COVID-19.

"We were really fortunate coming into this that we had laid the groundwork for data collection and data sharing," said Heatherington. "The technology platforms have been built. We have the capabilities."

Heatherington noted that rare diseases were the launching point for the data sharing component.

"Careful consideration around data sharing in rare diseases in particular has helped us understand what types of platforms, legal agreements and security measures for privacy are required," she said, although she noted that the process has been very slow in other indications.

Industry's momentum in the COVID fight is changing that now.

"It took months and months for people to share data before this, between the agreements and third party brokers. Trials

were finished before the data could be shared. But that work has enabled us to move rapidly into the galvanized industry. We have the technology and capability and now we're seeing modified behaviors to find out how quickly we can act in the face of the pandemic," Heatherington added.

The urgency of the pandemic means RWD is being shared at a faster pace, and Aetion CEO Carolyn Magill thinks the increased use of RWD will help the practice gain traction while fine-tuning the processes at the same time.

"More people will become familiar with how valuable these data are, and how more rapid cycle analytics and insights can impact clinical practice," she said. "The more we use real-world evidence, the more we'll understand about the strengths and limitations. That will better equip us to learn about how to apply it moving forward."

The next step will be finding ways to address the bottleneck when it comes to cleaning and interpreting the data, given the influx coming in from different sources ranging from electronic medical records and insurance claims.

"There's a typical lag time of at least a quarter and up to six months for real-world data curation, but now we don't have the luxury of waiting. Now we're getting data every two weeks, and the challenge is it's a lot more messy," said Gondek.

While the same level of data sharing and rapid drug authorization isn't likely to continue past the pandemic, Gondek hopes the progress made with real-world data will.

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