ROUNDTABLE SUMMARY

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Regulatory and Operational Challenges in European Clinical Trials for Korean Biotechs

James Jungkue Lee, CEO, Bridge Biotherapeutics
Jae-Young Ha, Senior Vice President, Research & Business Development, AriBio
Yooni Kim, Vice President, Clinical Services, Novotech
Elzbieta Rutkowska, Associate Director, Regulatory Affairs, Novotech

Moderator: Ian Haydock, Editor-in-Chief, APAC, Citeline

KEY TAKEAWAYS

- When locating clinical trials internationally, sponsors' main criteria are time, cost, and quality.
- Conducting clinical trials in Europe has clear advantages….
- … but conducting clinical trials in Europe also has unique challenges.
- Partnering with a CRO experienced in the EU market is crucial for surmounting challenges.

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OVERVIEW

Korean biotechs that wish to use an asset must carefully select where and when to conduct their clinical trials. While collecting data in the US is always a popular choice— due to this being a requirement of the US Food and Drug Administration (FDA)—Europe, too, is a location of interest thanks to its high quality of research, low costs compared to the US, and varied patient populations.

New regulations in the bloc may make life harder for these companies, though. Sponsors of clinical trials in the European Union (EU) that are expected to continue after January 30, 2025, must by that date transition registration of their trials to the Clinical Trials Information System (CTIS), a public portal and workspace for sponsors and competent authorities. The date marks the end of the three-year transition period that began when the Clinical Trials Regulation (CTR), which harmonizes the assessment and supervision of trials throughout the EU, went into effect.

CONTEXT

The panelists discussed the unique challenges biotech companies can expect to encounter when conducting clinical trials in Europe under the CTR and CTIS systems, as well as some of the advantages. Also discussed were the differences between conducting trials in different geographies within Europe, and the wider differences between Europe and the US.

This conversation took place during a live event at the Park Hyatt Hotel in Seoul, South Korea.

KEY TAKEAWAYS

When locating clinical trials internationally, sponsors' main criteria are time, cost, and quality.

The most significant time-based factor that determines sponsors' choice of location for their trials is a site's startup time, which refers to the time that elapses between the site first being identified and seeing its first patient. During this period, multiple key steps are performed: investigators are selected; regulatory and ethics submissions are made; and onsite training is performed.

The CTIS has harmonized these components across the EU, but some differences remain between countries, which means that selecting an individual country is still relevant.

> "We have to understand countries' cultural nuances in execution, because those are associated with time."
>
> *Yooni Kim, Novotech*

> "[Bridge Bio] planned to include Poland, Germany and Italy, in our studies. But Germany and Italy required some interesting additional data for submission, so we excluded those two countries, and included only Poland."
>
> *James Jungkue Lee, Bridge Biotherapeutics*

From a *quality* perspective, the main considerations are the availability of known, well-tested principal investigators (PI) and infrastructure. Europe, for the most part, does not struggle with these.

"When I review data from Europe, it always meets global clinical trial quality standards," Yooni Kim, Vice President, Clinical Services at Novotech, noted.

Sponsors, naturally, wish to keep costs as low as possible, without sacrificing quality. Countries in Eastern Europe are *generally* less costly than their Western European peers, yet trial feasibility evaluations do not always factor in the importance of costs. Inflation, however, is changing the European clinical trial landscape.

> "Eastern Europe is welcomed from a cost perspective, although it has shown high inflation in recent years. I have some examples of Korean biotechs and the big surprise of inflation in some specific Eastern European countries."
>
> *Yooni Kim, Novotech*

A slowdown in early-stage investment also limits biotechs' ability to perform trials in highly expensive locations.

> "Five years ago, we didn't have any concern about raising additional money to finance a project. In that case, cost might have been a minor consideration. But now [many biotechs'] financial situation is in such turmoil that cost might be the key factor."
>
> *James Jungkue Lee, Bridge Biotherapeutics*

Time and cost considerations, taken together, are particularly key for biotech companies developing novel treatments for rare diseases, given the small patient populations from which participants must be recruited. "We have limited patient resources to activate countries at affordable prices," said James Jungkue Lee, CEO of Bridge Biotherapeutics.

Additional factors sponsors and their clinical research organization (CRO) partners consider include disease demographics, local standards of care, local reimbursement levels, local regulatory environments, competing trials, estimated patient enrollment rates, market size, data integrity, and PIs' insights, experience, and capabilities, according to Jae-Young Ha, Senior Vice President, Research & Business Development at AriBio.

> "In designing a trial, in addition to selecting a country, it really depends on what the purpose of the study is."
>
> *James Jungkue Lee, Bridge Biotherapeutics*

Kim explained that South Korean biotechs are interested in international locations for their trials because market dynamics have evolved, and Korean companies have become more ambitious and competitive.

"In the past, Korean companies wanted to develop their product in South Korea first and then look outside. But the market has changed and biotechs are now looking to license globally and domestically at the same time," she said.

Lee added that part of this market change is due to investors who, now more than before, look globally for opportunities. "Look back to 2010 and the amount of money available to finance drug development from Korean investors and the government was very small. But after 2015 especially, private sector investors were really eager to finance Korean biotechs," he said.

Conducting clinical trials in Europe has clear advantages….

One of the principal reasons South Korean biotechs conduct clinical trials in Europe is the quality of the research ecosystem, including PIs and infrastructure.

"Many European investigators are ahead of the US in terms of industry research and science. That is associated with high-quality data, since they have a lot of experience with the infrastructure," Ha noted. In addition, the European Medicines Agency (EMA) tends to be more open and transparent in its communication with sponsors compared with the FDA, in his experience.

Sharing the same view, Elzbieta Rutkowska, Associate Director, Regulatory Affairs at Novotech, recalled an exchange with a US biotech sponsor who was awaiting an application assessment from the EMA and was expecting communication to consist of direct instructions and requirements. "They expected that if they don't answer immediately, the application would be rejected—and it's not like that," she said.

Part of the reason why the EMA is demonstrating such willingness to engage with sponsors is because there is a perception within the agency that the EU is falling behind the US and Asia in offering an attractive business and regulatory environment for clinical research, Rutkowska added.

> "I remember when I started [my career], calling the agency was a very difficult experience. Now I easily contact EMA or any national agency, including MHRA—it's just another call. They all are open to discuss and support."
>
> *Elzbieta Rutkowska, Novotech*

> "The EMA and FDA engage in healthy competition regarding regulatory processes."
>
> *Jae-Young Ha, AriBio*

In its efforts to ensure the EU remains competitive, the EMA has also become more curious about the regulatory frameworks of other regions, such as Australia, the US, and even developing countries. "The EMA has awakened to [the importance of] innovation drivers," Kim observed.

Ha added that, since the EMA moved the location of its headquarters from London to Amsterdam, the agency has improved its communications to sponsors. "In my opinion, the EMA are focusing on this area very much to improve because of the national culture of the Dutch people. They are very structured and much more precise than the English in general," he said.

Because the CTR defines fixed timelines for regulatory approval decision making, much like how the FDA does in America, CROs can now be much more specific with sponsors regarding timelines. In addition, Kim explained that the EU's regulatory environment is attractive due to its strong intellectual property (IP) protections. Last but not least, conducting trials in Europe is often easier compared to the US because of the diversity of its patient populations—an aspect that is increasingly important to regulators globally.

"CTR is applicable to all EU and EEA countries. We still have different languages and some additional national requirements, but we are following the same legislation, the same regulation," Rutkowska added. "So conducting trials in the EU is already more streamlined."

… but conducting clinical trials in Europe also has unique challenges.

However, carrying out clinical research in the EU is not without challenges. One of them is the high cost of running trials in Western Europe, which has long been the default destination for trial sponsors. With Central and Eastern European (CEE) countries steadily improving their research infrastructure, know-how, human capital, and reimbursement levels for novel treatments, and with the pharmaceutical market in those regions experiencing higher growth than in Western Europe, an increasing number of biotech companies are considering going East.

Due to their higher levels of economic development, West European countries also have the disadvantage of being unable to provide sponsors with significant numbers of treatment-naïve patients, hindering recruitment efforts. And once a trial begins, medical and diagnostic practice—which may impact how effectively trials are implemented—tends to be different in CEE countries from those in Western Europe.

Lee gave idiopathic pulmonary fibrosis (IPF), a condition in which the lungs become scarred without obvious cause, as an example where "on paper it looks the same" between different nations, yet differences persist. "In the US, IPF is typically diagnosed based on some interdisciplinary group decision consisting of a pulmonologist and a rheumatologist and some other disciplines. In Europe and Korea, most cases are diagnosed by a pulmonologist alone."

Ha elaborated on this point further. He noted that AriBio, which is developing a platform for the treatment of neurological diseases, conducts most of its Alzheimer's disease research in the US for two major reasons.

First, he said that the FDA is one of the most advanced regulatory bodies in the world that has a "streamlined and refined" definition of Alzheimer's, adding that, on a geographic scale, how it is recognized and diagnosed varies drastically.

Ha further explained that diagnosis of Alzheimer's disease is incredibly subjective, with most assessments relying on questionnaires designed to interrogate a patient's memory and cognition. Using fruit as an example, he said that a questionnaire in one country might contain an apple, and in another, a banana.

Merely standardizing this across all countries would not work since "some people may have never seen a banana, especially the elderly… it is very difficult to communicate with patients identically in different countries." As a result, AriBio performs its research in the location with the largest number of market-relevant patients, the US.

Another obstacle faced when conducting studies in Europe is that occasionally PIs will overpromise and underdeliver in terms of patient recruitment, which may not only delay trials but also add costs to biotech companies' already stretched budgets.

Another challenge is the multitude of languages spoken in Europe, which increases compliance costs and burden for sponsors as they have to translate most Part II documents, such as informed consent documents, into multiple languages.

Partnering with a CRO experienced in the EU market is crucial for surmounting challenges.

Many of the difficulties of conducting clinical trials in the EU can be addressed by partnering with a CRO that has local experience, expertise, capabilities, and teams at the country level.

> "Novotech's European team has country management teams in more than 20 countries, so we have the additional values of local input."
>
> *Yooni Kim, Novotech*

For example, the way Novotech prevents overpromising and underdelivering on trial participant recruitment numbers is by studying historical data related to PIs' and study sites' recruitment patterns. Novotech country managers also have regular contact with PIs to check on ongoing studies and ensure they are progressing as planned; the information is then shared with sponsors.

Another way Novotech supports Korean trial sponsors conducting studies in Europe is by ensuring all processes are compliant with the General Data Protection Regulation (GDPR), the EU's sweeping and often onerous data protection regulation. "We can take up these responsibilities and not just the responsibility of delivering [a trial]," Kim said.

> "As a CRO, you have to train Korean biotech companies on those aspects—it's such a revelation for them."
>
> *Jae-Young Ha, AriBio*

CONCLUSION

Going forward, the panelists said they expect conducting clinical trials in the EU under CTR and CTIS to become easier and more streamlined, especially after current flaws in CTIS related to transparency and documentation have been ironed out.

One area they see as having great potential but that remains a challenge—in the EU as much as in other regions—is the need to develop validated clinical endpoints and digital biomarkers for trials that use sensor-equipped mobile phones and wearable devices to track a patient's health condition in real time.

To make the most of these expectations when they materialize, sponsors need to stay on top of regulatory updates, trends, and requirements—and, ideally, have a reliable CRO partner to support them along the way. "People have to be trained, they have to be experts, and we need to also provide this training to our sponsors," Rutkowska concluded.

BIOGRAPHIES

James Jungkue Lee
CEO, Bridge Biotherapeutics

James Jungkue Lee founded Bridge Biotherapeutics Inc. in 2015 and currently serves as the CEO. After receiving his B.S. and M.S. in Structural Biology from Seoul National University, he held various roles in research, research planning, and business development at LG Chem. After his tenure at LG Chem, Lee co-founded Crystal Genomics where he led fundraising and business development activities. In 2008, he founded Rex Bio and successfully developed an antibody treatment for pancreatic cancer.

Jae-Young Ha
Senior Vice President, Research & Business Development, AriBio

Jae-Young Ha is a seasoned pharmaceutical executive with over 35 years of international experience. His expertise spans research, regulatory affairs, marketing, and business development in markets including Europe, the Middle East, and Asia. He has held senior leadership positions at Novartis and CSL Behring, where he played a pivotal role in the development and launch of new pharmaceutical products. Ha holds a B.S. and M.S. in Pharmacy from Seoul National University and is a QPPV and RP at both MHRA and the EMA. Currently serving as Senior Vice President of Research and Business Development at AriBio, he oversees the development of groundbreaking oral treatments for Alzheimer's disease, including AR1001, which is currently in Phase 3 trials globally.

Yooni Kim
Vice President, Clinical Services, Novotech

Yooni Kim is the Global Head of Clinical Services at Novotech, with over 25 years of clinical research experience and technical knowledge in CROs, pharmaceutical companies and academic research institutions. With a Ph.D. in Preventive Medicine (Epidemiology) from the Seoul National University of Medicine, she started her career at GSK in 2004 and joined ICON Clinical Research (formerly PRA) in 2009 as Director of Operations. Kim worked with PRA Health Sciences for seven years, establishing the legal entity and service capabilities for PRA Korea. After joining Novotech in 2016, she served as the Executive Director Asia Operations. Currently, she continues to lead Global Clinical Operations at Novotech.

Elzbieta Rutkowska
Associate Director, Regulatory Affairs, Novotech

After completing a master's degree in human nutrition and home economics at Poland's Warsaw Agricultural University (now the Warsaw University of Life Sciences) Elzbieta Rutkowska went on to work at AstraZeneca as a clinical data assistant. Following this, she moved to Covance, working her way up to become a senior specialist at its global regulatory submissions department. In 2022, she joined EASThorn, which was acquired by Novotech in 2023, where she serves as the associate director of regulatory affairs.

Ian Haydock (Moderator)
Editor-in-Chief, APAC, Citeline

Ian Haydock has been covering a broad range of topics across the Japanese and Asian pharma industry, including corporate, M&A, R&D, pricing and policy developments, since 1988. After a stint as Tokyo-based Japan and Asia editor for Scrip, in 2014 he became managing editor of PharmAsia News (now part of Scrip/Pink Sheet). In his current position, he directs regional coverage for Scrip and Pink Sheet and manages a multinational, on-the-ground team. Haydock is a recipient of multiple internal and external awards and a regular participant in APAC conferences, webinars and events, and produces regular podcasts.