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India Trials And Tribulations: J&J, IQVIA Execs Offer Potential Solutions

by Anju Ghangurde

Real and perceived barriers have bogged down the Indian clinical trials segment. Senior leaders of J&J, IQVIA and 5AM Ventures say many COVID adaptations should be codified, while a member of India's NITI Aayog indicates an openness to find solutions to some pain points.

A cross-section of biopharma experts deliberated at a recent summit what's holding back foreign sponsor interest in clinical trials in India and sought to address some of the "hurdles" and "perceptions" that are currently weighing things down.

Peter Ronco, head of global development, Janssen Research and Development, *Johnson & Johnson*, emphasized the need to "embed" many of the changes and innovations that the Indian regulatory system was forced to adopt during COVID-19 and which have helped drive advances in the clinical trial landscape.

"Great innovations that we need to maintain are things like how do we optimize the speed of review of regulatory packages, which is such a critical part of having a competitive advantage in terms of how India is competing with other countries around the world for clinical trial populations," Ronco said at the USA-India Chamber of Commerce (USAIC) annual Biopharma and Healthcare Summit. (Also see "*ISCR's Davis On Pandemic Adaptations, Value Of Multi-Regional Trials*" - Scrip, 26 Apr, 2021.)

Moving more to online reviews and "having those kind of datasets and data sources" accessible online need to become the "standard operating procedure" for working with India, while continuing to "grow into" some of the global standards and ways of working, the executive said.

India had, like several other nations, provided certain regulatory flexibilities amid COVID-19-related uncertainties. For instance, its Central Drugs Standard Control Organization (CDSCO) released various orders to fast-track all proposals pertaining to the pandemic. Among others, the

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regulator issued in late March 2020 a specific notice around handling cases of protocol amendment/deviation/modification in procedures which may have become necessary due to unavoidable circumstances amid the situation. (Also see "*Indian Trials Recover Amid Lingering Pandemic Challenges*" - Scrip, 7 Dec, 2020.)

J&J's Ronco, however, indicated that the core concern for foreign sponsors revolved around "instability" and changes in regulations.

"The biggest perception I continue to hear is 'yeah it's good now but it could go down tomorrow, the next month, next year.' The more we can do to message stability in the regulatory environment, I think is the first [thing]," Ronco said at the session, which was moderated by Andrew Plump, president of R&D, *Takeda Pharmaceutical Co. Ltd.* (Also see "*Amgen, J&J, Takeda R&D Heads On The Era Of Human Data, Treating Disease Earlier*" - Scrip, 4 Jul, 2022.)

Large Book Of Work In War-Hit Region

Importantly, Ronco also highlighted potential near-term opportunities for the Indian clinical research segment against the backdrop of disruptions amid the Russian-Ukraine conflict. J&J had a "large book of work" in the war-torn region and has not able to run that research anymore.

"We had about 60 to 70 studies running in Ukraine at the point of the invasion and so we are now looking as a company about how we move that book of work elsewhere around the world," Ronco said.

In addition, there continue to be lockdowns and additional COVID-19 outbreaks in a number of countries, which restrict the patient population there.

"Those geopolitical and healthcare issues around the world do provide an amazing opportunity for India. I'm seeing a lot more of an interest coming from our global teams in terms of really looking to invest and grow and develop."

Commercialization, Compensation Issues

The summit also provided some telling insights around why sponsors may be shying away from placing trials in India.

Compensation Norms 'Soft And Friendly'

The Indian government machinery is keeping a close eye on developments in the clinical research segment, with the country keen to emerge as a preferred destination and "ethical hub" for trials.

It is also seen as a segment that could "enrich" India's own science, academia and the nation itself, with an executive from NITI Aayog indicating at the USAIC summit a willingness to feed back into the system the

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Dr Cynthia Verst, president, Design and Delivery Innovation, R&D Solutions, *IQVIA*, indicated that in areas where the firm operates, the top reason for getting "declinations of India" is due, in part, to the "commercial strategy of sponsors, and not intending to market their product in India."

The other leading reasons for sponsor reluctance are concerns around the regulatory landscape in India and the "compensation component" and also the "perception" of lower quality, the executive said, even as she highlighted IQVIA's strong run for clinical research services in the country.

In response, Vinod Paul, member of India's NITI Aayog, a government policy think tank, indicated an openness to consider addressing some of the pain points. (*See side box.*)

Verst, however, subsequently explained that it is perhaps a "misperception" to view the compensation clause as a huge barrier, going by actual evidence as highlighted in some publications, wherein "there are very few incidents, and the compensation requirement was not extremely excessive."

In September last year, *The Wire Science* reported that in the last 10 years (2011-20), 311 participants died because of clinical trials in India and 22,176 experienced "non-lethal side effects" that required hospitalization. Average compensation of INR843,533 ($10,666) was awarded for a trial-related death, the concerns of stakeholders and also to find solutions to pain points, where possible.

Touching on India's trial compensation provisions that have long made sponsors nervous, NITI Aayog's Vinod Paul maintained that the norms are now "much more soft and friendly."

With panelists at the summit referring to the compensation issue as an area of concern, Paul said he was keen to understand if the current rules are still not something which is a "global norm."

"What is it that we can do more about? I thought it's quite reasonable, a balance. If you think there is still an issue, we can try to understand that and find a way forward. But if it is a balance, given India's democratic moorings, civil society, courts and law, then let's celebrate the success that we can pull."

Paul, who has been part of the core team of the Indian government styling the country's COVID-19 response, further noted that in the case of academic clinical trials, the regulatory pathways in India are "even more green-signalled."

"So there is a change, we are willing to make more changes. … The point remains that these changes and accelerated changes during the COVID-19 pandemic show the intent of the government to 'walk the talk,'" he added.

Paul also highlighted the clinical trial

report said, citing CDSCO data.

Related to the intent to market/commercialization component of India, IQVIA's Verst flagged the need to address requirements around having a specific percentage representation of the Indian population for certain studies and also a mix of public versus private investigator sites in the country.

"I think these are in fact the opportunities that we have and in terms of sharpening and honing the information and guidance regarding the intent to market in India in that commercialization component," Verst said.

Th executive indicated, however, that the Indian regulator has been open to addressing stakeholder concerns pertaining to some of these challenging requirements.

"When we are able to bring pragmatic rationale and evidence suggesting that we need to go more private than public due to the representation, there has been very sound and very collaborative approaches with the regulatory authorities," she observed. (Also see "*IQVIA Biotech's Sockalingam On Clinical Research Virtualization In APAC*" - Scrip, 7 Jun, 2021.)

networks initiative rolled out by the National Biopharma Mission under the aegis of the Department of Biotechnology. The network, comprising a consortia of hospitals in the areas of oncology, ophthalmology, rheumatology and diabetology, aims to strengthen the capacity to conduct clinical trials in India for products developed in these areas. It covers several public and private hospitals, clinics, academic institutions across many states of the country.

"These are sites that are ready, people are trained in principle to be able to conduct the studies and that's something very useful. We used these trial sites for fast-tracking COVID-19 vaccination studies, not only of Indian vaccines but also those that were tested in our country, but developed elsewhere," Paul explained.

Similarly, last year, the Indian Council of Medical Research launched the Indian Clinical Trial and Education Network (INTENT), which intends to create capacity, pathways and offer partnerships across institutions and other academic institutions in the country. It aims to provide evidence-based, robust and "culturally sensitive" solutions to urgent health problems, in a reasonable time frame, by conducting large multi-center clinical trials.

Biopharma industry experts in India similarly highlighted to the *Pink Sheet* that requirements around patients numbers, as well as public versus private investigator sites, are not really cast in stone in the norms.

India's New Drugs and Clinical Trials Rules, 2019 broadly state that the "number of subjects to be included in the clinical trial should be adequate depending on the nature and objective of the

clinical trial." (Also see "*India's New Trial Rules Tick Right Boxes, Shed Interim Compensation Clause*" - Pink Sheet, 31 Mar, 2019.) (Also see "*India New Trial Rules - Sponsors Interested But 'FAQ' Could Help*" - Scrip, 16 Apr, 2019.)

One expert explained that CDSCO used to typically insist on trials in around 100 patients for an Indian marketing approval and this figure went up to 200 for comparative trials.

"So if a global trial includes 1,000 patients and the sponsor wants to use this data for Indian approval, inclusion of 250 patients looks reasonable and feasible for common chronic diseases. However, it would be difficult to include an adequate number for clinical trials where the patient population could be small e.g. advanced cancer patients with positive biomarker, rare or orphan conditions," the industry veteran explained to the *Pink Sheet*. (Also see "*India Tweaks More Trial Rules But Can It Change The Narrative?*" - Pink Sheet, 5 Aug, 2016.)

Further, following past trial-related public interest litigation in India, there have been increased regulatory compliance requirements for investigators as a result of which the number of investigators who are willing to participate in clinical trials has probably shrunk.

"This could make inclusion of 25% Indian patients quite challenging for the sponsor. Ethics committees also decide number of trials per investigator," he added.

Not 'Insurmountable Hurdles'

The USAIC summit also saw Kush Parmar, managing partner, 5AM Ventures, drive home the point that while the Indian market may have its own set of "hurdles" to overcome these aren't really "insurmountable" as evidenced by Immuneel Therapeutics, which recently begun patient dosing in its IMAGINE CD-19 CAR-T trials in India. (Also see "*What's Next At Dr Reddy's: Biologics CDMO, Cell And Gene Therapy Push*" - Scrip, 27 Jun, 2022.)

Immuneel, a start-up focused on creating access to CAR-T and other cellular immunotherapies for the management and treatment of cancers, was founded in 2019 by *Biocon, Ltd.* founder and chairperson Kiran Mazumdar-Shaw, US oncologist Siddhartha Mukherjee and Parmar.

The Immuneel endeavor, Parmar said at the summit, started during a "very agitated dinner" two and a half years ago and things reached a crescendo over the course of the evening talking about the fact that in an established modality like CAR-T – which had been available around the world for eight to 10 years – there were no commercial products available in India and not even a single patient dosed with a CAR-T in a clinical trial. (Also see "*It's Coming Home: ImmunoACT Advances Plans For Cut-Price CAR-T In India*" - Scrip, 30 Jun, 2022.)

"That was just unconscionable and I think crazy," said Parmar, who is a director at several firms including *Rallybio* and Vor Biopharma.

The executive referred to some internal hurdles and perceptions along the way, given that Immuneel was advancing a very complex modality and a Phase I/II study in a setting like this is "highly innovative and has a lot of unknowns." Moreover, the regulatory science is new as well in India.

"The second piece, not surprisingly, for a complex modality is there were a lot of agencies to work with. I think there was a lot of streamlining that absolutely could have got us into the clinic even sooner, because of the lack of communication between different agencies," he said.

Nevertheless, Parmar underscored that Immuneel is "a product of collaboration" with the regulators and also external experts, for something that is a new modality and where most of the clinical and regulatory experience has been outside of India.

"How do we just make sure we're opening the door to that kind of collaboration so we can maintain rigor and quality on international standards within India as well? " he asked, reiterating that there may have been some hurdles but "not fundamental barriers."