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Innovent/Lilly's Sintilimab, Developed In China, May Be Headed For Troubled US Waters

by Sue Sutter

Ahead of advisory committee, FDA officials raise concerns about the PD-1 inhibitor, which was submitted on the basis of a Phase III trial conducted solely in China. OCE's Pazdur and Singh make the case for a global, harmonized approach to cancer drug development using multiregional trials.

The US Food and Drug Administration is signaling concerns about relying on Phase III data generated in a single country ahead of a 10 February advisory committee review of *Innovent Biologics, Inc.*/*Eli Lilly and Company*'s PD-1 inhibitor sintilimab in non-small cell lung cancer.

In a comment published in Lancet Oncology on 4 February, Oncology Center of Excellence leaders Harpreet Singh and Richard Pazdur say the sintilimab application raises questions regarding use of data from a single country – in this case, China – to support approval and its generalizability to the US population.

"The degree of regulatory flexibility in establishing the acceptability of data from a single country and its generalisability to a new population should be balanced against the drug's innovation," the comment states. "Other factors establishing whether a single country foreign submission would be acceptable and whether there is a need for a bridging study include the trial's endpoint compared with endpoints used to support previous US approvals, the size of the trial population, and the disease prevalence in the USA compared with the foreign region."

Singh, OCE's associate director of oncology in older adults and special populations, and Pazdur, OCE's director, lay out the challenges that Innovent and Lilly are likely to face when sintilimab goes before the Oncologic Drugs Advisory Committee on 10 February.

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The mere publication of the article is a reflection of Pazdur's publicly stated view of the importance of "bringing the community along" before an advisory committee – in essence, setting the stage for the panel discussions to follow. (Also see "*Accelerated Approval Makes Big Splash In 2021 Novel Agents, Despite Crackdown On 'Dangling' Cancer Claims*" - Pink Sheet, 18 Jan, 2022.)

In their article, "Importing Oncology Trials From China: A Bridge Over Troubled Waters?", the OCE leaders also make the case for a global, harmonized approach to cancer drug development based on multiregional clinical trials (MRCTs) and coordinated regulatory submissions.

Not An Isolated Case

Sintilimab is under standard review, with a March user fee goal date, for first-line treatment of non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy. The BLA is based on the Phase III ORIENT-11 study conducted solely in China.

"The trial's design, patient population, and statistical analysis closely resembles landmark NSCLC trials that established checkpoint inhibitors as part of initial treatment regimens several years ago," the OCE leaders say.

Pazdur has previously said marketing applications that rely on patient data from a single country are "problematic" and run counter to US efforts to increase the patient diversity in clinical trials. He also has expressed frustration with the proliferation of "me too" drugs in the PD-1/L1 space. (Also see "*China-Only Studies Are 'Problematic,' US FDA's Pazdur Says Ahead Of Lilly/Innovent PD-1 Inhibitor Review*" - Pink Sheet, 16 Dec, 2021.)

These concerns are reiterated in the Lancet Oncology piece.

Rather than being an isolated case, the sintilimab application "reflects an increasing number of oncology development programmes based solely or predominantly on clinical data from China, with at least 25 applications from China in drug development phases, planned to be submitted, or currently under review."

ICH E5 Considerations

The article discusses International Council for Harmonisation guidelines on acceptance of foreign data and multiregional clinical trials.

The ICH E5 document provides a framework for assessing the acceptability and generalizability of clinical data gathered outside a region by evaluating both intrinsic and extrinsic aspects of that data.

Intrinsic factors include genetic and physiological variables, such as polymorphisms, lean body

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mass, organ dysfunction, differences in causes, histologically and molecularly defined disease subtypes, and known determinants of response to therapy. Extrinsic factors that are considered include medical practice, available therapies, social and cultural determinants such as diet, and concomitant herbal medications.

Depending upon the degree of difference in these factors between the region where the trial was conducted and the country where drug registration is sought, it is possible that no further studies may be necessary. However, it is also possible that bridging studies or controlled trials to support the intended indication could be required by a regulatory authority.

> ***"Since trials coming from a single foreign country will generally have differing ethnic and racial representation in the population compared with the USA, additional data should be provided to ensure the generalisability of their results to the US population." – FDA's Harpreet Singh and Richard Pazdur***

"The current influx of applications containing trials that have enrolled patients exclusively or predominantly in China might have limitations not envisioned in E5," Singh and Pazdur state.

In addition to differences in intrinsic and extrinsic factors, studies conducted to bridge from the Phase III trial in a single region to another country's population and medical practices might not fully address concerns regarding generalizability, the authors said. Bridging studies are smaller, tend not to be randomized, and rely on response rates or pharmacodynamic comparisons rather than the harder endpoints used in the multiregional clinical trials.

"This regulatory flexibility in accepting bridging studies rather than mandating an additional controlled trial to establish safety and efficacy has been justified in previous decades for drugs that had few alternatives and generally fulfilled an unmet medical need," the authors said.

However, many of the current applications that rely on clinical data from China are similar to previously conducted multiregional clinical trials that led to US approval of other drugs and, consequently, do not fulfill an unmet need, the article states.

The authors suggest a greater degree of regulatory flexibility might be shown for a large trial investigating a disease more common in Asia, such as hepatocellular carcinoma or nasopharyngeal cancers, especially if an improvement in overall survival is shown.

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“Trials relying solely on enrolment from a single country might have less ethnic and racial representation relevant to the US population, notably with regards to currently underserved groups,” the article states. “Sponsors should prospectively address measures to ensure the representation of patients reflecting the population who will eventually use the product in the USA.”

“Since trials coming from a single foreign country will generally have differing ethnic and racial representation in the population compared with the USA, additional data should be provided to ensure the generalisability of their results to the US population.”

Regulatory Interactions Build Confidence

The OCE officials also highlight the importance of previous regulatory interactions between the US and a foreign country, the degree to which might influence the evaluation of, and confidence in, submissions from that locale.

“The extent of past participation in MRCTs might provide added confidence in trial conduct and data integrity,” the article states. “Since some clinical site inspections cannot fully capture the heterogeneity of data quality and study conduct across many clinical sites, previous participation in MRCTs and previously reported data integrity challenges might be factors in establishing the need for further trials.”

This could be especially true during the current COVID-19 pandemic, which has severely limited the FDA’s ability to conduct on-site inspections of clinical trial sites and drug manufacturing facilities.

The extent of a sponsor's interactions with the foreign regulator also are important, the FDA officials say.

Many sponsors seeking US approval based solely on data from China have not sought regulatory advice from the FDA through established milestone meetings, Singh and Pazdur said. “Trials have been done in China using comparators that are not representative of the current US standard of care and would have difficulty in enrolling patients where advances have been approved and widely accepted by practitioners.”

The article touts a role for OCE’s Project Orbis, which allows for concurrent regulatory submissions and reviews across multiple countries, to help reduce the delay in foreign countries’ access to new therapeutics. Pazdur previously has discussed the idea of inviting China to be part of Project Orbis, while acknowledging that intellectual property and confidentiality issues would first need to be addressed.

The ICH 17 guideline, issued in 2017, reflected a consensus that trials requiring international

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collaboration were preferred over single country trials for drug registration purposes. MRCTs foster more efficient drug development, avoid duplication, allow earlier access to innovation and establish new standards of care more quickly.

“The true bridge over so-called troubled waters for global drug development and regulatory harmonisation will be MRCTs rather than single country trials,” the OCE leaders say. “MRCTs can be strengthened by providing support and welcoming countries, such as those in Africa and Latin America, currently underrepresented in oncology MRCTs. This greater diversity might provide additional information to assist the USA in addressing the underrepresentation of racial and ethnic minorities in drug development.”

“Participation of a greater number of countries in MRCTs will provide a framework to establish experience and trust in the evidence supporting applications and might create a long-lasting bridge between patients, health care professionals, and regulatory agencies of different nations in expediting future advances,” Singh and Pazdur conclude.

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