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## India Clinical Trial Policies Are Aligned With Industry's Goals – MOH Official

*A Ministry of Health official addressed concerns that India's clinical trial policies are an impediment to local innovation and asserted that the country wants clinical trials to take place to address large unmet health needs.*

CAMBRIDGE, Mass. and MUMBAI – Saying he felt “fortunate” to speak to an industry audience that had highlighted clinical trial policies and infrastructure as the biggest obstacles to Indian innovation, a key government official recently said India's goals are aligned with the goals of the pharmaceutical industry.

“We are on the same page. We want investment. We want innovation. We want clinical trials to take place,” said Ravinder Kumar Jain, additional secretary and director general, Central Government Health Scheme in India's Ministry of Health & Family Welfare.

“Our intention is that we would like a clinical trial to be carried out in India in the same manner in which it is done elsewhere,” Jain said, noting that India needs new medications tested in-country to address its large unmet health needs. But he also acknowledged that the government must do a better job to explain the rationale for recent changes to India's clinical trial policies.

Jain spoke June 21 during the USA-India Chamber of Commerce's (USAIC's) annual biopharma and health care summit in Cambridge, Massachusetts. As part of the event, USAIC commissioned a 150-page report, authored by McKinsey & Co., entitled, “Will India Play A Meaningful Role In Global Biopharma Innovation?” A key finding of the report is that clinical trial policy and infrastructure is the biggest obstacle to driving Indian innovation, despite recent news flow focusing on intellectual property protection (*“Sneak Preview: Clinical Trial Policies Top IP As Biggest Obstacle To Indian Innovation” — PharmAsia News, Jun. 19, 2013 4:53 PM GMT*).

### Overhaul Of Process

India has seen a significant decline in clinical trials over the last two years in the wake of a public uproar over medical research and related policies on informed consent, compensation to injured patients and the role of ethics committees.

### What Are The Biggest Obstacles That India Faces In Driving R&D At Scale?

Clinical Trial Policy & Infrastructure	80%
Research Talent	60%
IP	30%
Funding	20%

Source: McKinsey & Co., USA-India Chamber of Commerce report: “Will India Play A Meaningful Role In Global Biopharma Innovation?” Based on a survey of 30 senior U.S. and Indian biopharma leaders; % is percentage of respondents that answered.

The industry said it has been damaged further by a perception, enflamed by local media, that Indian patients are used as “guinea pigs” by multinational companies (*“ACRO Chairman Apurva Shah On New Guidelines For Clinical Research In India: An Interview With PharmAsia News” — PharmAsia News, Sep. 21, 2012 5:00 AM GMT*).

In early January, India's Supreme Court came close to halting all clinical trials in India, relenting only after an assurance from the government that the health secretary would personally monitor implementation of a stricter regulatory regime and crack down on malpractices (*“Faced With An Adverse Verdict, India's Clinical Research Industry Pushes For A Quick Makeover” — PharmAsia News, Jan. 4, 2013 7:04 PM GMT*).

Still, the court's intervention has had a chilling effect on new clinical trial approvals. The Drug Controller General of India approved only six clinical trials for new chemical entities since January until a recent round of approvals announced last week, according to a report in the India business paper Mint. The Supreme Court is scheduled to hold a follow-up hearing July 26 to review the government's progress on clinical trial reforms (*“India Approves 50 New Clinical Trials Ahead Of Supreme Court Review” — PharmAsia News, Jul. 3, 2013 3:14 AM GMT*).

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The government established an expert committee to look into all aspects of the clinical trial process, from regulations and procedures to how many clinical trial sites should be approved, Jain told meeting attendees.

One reform that has generated controversy is a new rule to compensate patients injured in clinical trials. Stakeholders in the clinical trials industry have claimed the rules would make studies impossible to conduct as companies could be held liable if a patient receives a placebo, or if an investigational product fails to provide its intended therapeutic effect (*"India's Compensation Rules For Clinical Trials May Make It Impossible To Build Data: Indian Society Of Clinical Research"* — *PharmAsia News*, Feb. 6, 2013 4:12 PM GMT).

The recent changes are intended to provide "transparency in the entire process of clinical trials," according to Jain, so that sponsors know what is required and how long approval will take. The changes will also ensure that India protects the rights and safety of study participants, he said.

Between 2005 and 2012, more than 2,800 patients died while participating in clinical trials in India. Among those deaths, the Indian government concluded that 89, or less than 3%, were directly related to the trial itself, Jain said.

Although a small percentage, "it is very difficult for us as regulators and policymakers to answer why these 89 people have not been paid compensation," he said. While some families have been paid, it often takes several years, he explained. "Even today, there are people who died in 2006, 2007, who have not been paid compensation."

In addition, the amount of compensation is generally "meager," Jain said, explaining that in the majority of cases, compensation is between \$3,000 and \$7,000.

"It is our duty to ensure that when you register a subject, you must have his address, you must have the name and the address of the nominee, so in the case of death someone can be paid the amount," Jain said. "And it is our duty to ensure that timelines exist on the part of everybody associated in the process of clinical trials to take certain actions," he added, singling out principal investigators, ethics committees and sponsors.

"The timeline has to be reasonable, but there has to be a timeline. Why should we not decide the timeline for the people who must pay compensation? This is what we've done," he said.

Jain also emphasized that the process must be transparent so that the potential liability for a sponsor is clear and not "open ended." The government is developing a formula to determine the amount of compensation for clinical trial victims, he said, citing the patient's underlying health as one factor to consider.

#### **Stakeholder Concerns**

"The changes that we've done were after wide consultations," Jain said. "All stakeholders were consulted. They were put on the website. Comments were invited."

But the official also acknowledged that some stakeholders have expressed concerns. The government forwarded several of the top concerns to its Drug Technical Advisory Board (DTAB), an influential group of experts from prominent health authorities, for further review. "We are in the process of having a look at them," he advised.

In a discussion with *PharmAsia News* after his talk, Jain declined to provide a timeline for when the government may revise the guidelines based on stakeholder concerns and the DTAB review.

In particular, industry stakeholders have raised concerns about the compensation guidelines. The guidelines provide for compulsory free medical benefits to those injured in the course of trials, as long as required.

#### **Distinction Needed For Trial-Related Injuries**

The Indian Society of Clinical Research (ISCR), which represents accredited contract research organizations, has objected to the point noting that "a blanket provision would act as an inducement and prevent a potential subject from exercising better judgment while considering participation in a clinical trial." Also, ISCR said no distinction has been made in the notification between a study-related injury and a non-related injury suffered by a clinical trial subject, such as a traffic accident or an accidental fall.

Another issue raised by ISCR is about compensation to be paid in the case of an injury or death due to failure of the investigational product to provide an "intended therapeutic effect" or use of placebos in placebo-controlled trials. ISCR maintains that the rule contradicts the scientific basis of a clinical trial and would have a far-reaching impact on organizations and academic institutions, both Indian and multinational.

By definition, ISCR said, a clinical trial is conducted to learn whether an investigational product has the intended therapeutic benefit, so the guidance contradicts the very essence of a clinical trial. The group also noted that "intended therapeutic benefit" could be open to broad interpretation, particularly for determining endpoints in oncology trials.

ISCR also highlighted clauses that deal with injury arising out of a placebo-controlled trial. In its comments, the CRO industry group noted a placebo is not meant to have any therapeutic effect, and placebo-controlled trials are closely monitored by the New Drug Advisory Committee (NDAC) prior to clinical trial approval.

"Moreover, approvals are granted only if the NDAC is satisfied that a placebo-controlled trial would not compromise the safety of trial subjects. In addition, it is the duty of the ethics committee to examine the protocol and determine whether it would be ethical for a placebo to be used in a study and to ensure there are built-in mechanisms to monitor the health of trial subjects," ISCR said.

#### **Critical Changes On Hand**

The lobbying pressure seems to be having some effect on reaching clarity. DTAB held a meeting May 16 where it

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emphasized the need for major changes to ensure continued clinical research in India. A technical committee constituted on orders of the Supreme Court to look into issues related to clinical research, DTAB said that providing free medical management to an injured subject, irrespective of whether the injury is related to the clinical trial, should be amended to ensure that medical management is provided in the case of “injury due to clinical trial-related activities only.”

DTAB further said the clause relating to financial compensation in the case of injury or death due to a failure of the investigational product to provide the intended therapeutic effect should be “deleted.”

“Similarly in the case of placebo-controlled trials, the eligibility for compensation should be in the case of injury or death due to use of placebo in a placebo-controlled trial if the standard care is denied. That apart, the timeline requirements for submission of serious adverse events report after due analysis by the sponsor/investigator should be harmonious to the international practice of 14 calendar days instead of 10 days as prescribed.”

The government advisory board also recommended that in the case of investigator-initiated institutional trials, the department of health research “should maintain ... funds to compensate subjects who suffer injury or death during such institutional clinical trials.”

DTAB noted at its May 16 meeting that if injury to a trial subject is related to the clinical trial, he or she will also receive financial compensation as per order of the licensing authority defined under rule 21(b), and the financial compensation will be over and above any expenses incurred on the medical management of the subject.

The board recommended that a qualifying clause be added in the sub-rule that in case there is no permanent injury, the compensation shall be commensurate with the inconve-

nience, loss of wages and transportation costs (See: *DTAB Meeting Minutes May 16 2013*).

On provisions related to the use of placebo in a placebo-controlled trial, DTAB agreed to the suggestion of the technical committee that in certain cases, a placebo-controlled trial is necessary to evaluate the efficacy of an investigational drug. The lack of therapeutic effect for a placebo should be explained to the subject during the informed consent process, DTAB said.

However, some stakeholders concerns, such as requiring an investigator to report serious adverse events to the licensing authority and others within 24 hours of occurrence, was not agreed to by DTAB, and it did not recommend changes.

ISCR President Suneela Thatte said in a statement that DTAB’s findings are an encouraging development. “Collaboration, transparency and open dialogue are important to ensure the progress of the industry, while securing the rights and safety of patients,” she said.

The current compensation rules, according to Thatte, “makes the continuing conduct of high-quality, scientifically valid clinical trials in India virtually impossible, negatively impacting the availability of scientific data to assess the benefits and risks of medicine for the Indian population. We believe that all of these contentious rules need to be addressed with equal priority and emphasis.”

Thatte also advocated for a faster approval process for clinical trials in India. She lamented that although India was home to one-sixth of the world population, only 1.5% of clinical trials are undertaken in the country, impacting local medical research institutions and depriving the benefits of research to Indian patients.

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