Original Article

# A two-year evaluation of the minutes of Investigational New Drug committee meetings

Jeffrey Pradeep Raj, Nithya J. Gogtay, Urmila M. Thatte

Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

## Abstract

**Introduction:** The Investigational New Drug (IND) committee advises the Drug Controller General of India on matters pertaining to clinical trials (CTs) of IND for clinical development. An audit of the minutes of this committee's meetings would shed light on the drug discovery in India.

**Methods:** Minutes of the IND committee meetings available in the public domain (2-year period) were evaluated. The applications which were postponed were excluded from the study. Outcome measures were therapeutic areas of IND, purpose of the applications, status of registration with the CT Registry of India (CTRI), and the innovator country.

**Results:** The minutes of $N = 7$ meetings were available in the public domain for the period January 2017–December 2018 with $N = 45$ agenda items. One agenda item was excluded, and $n = 44$ agenda items were finally analyzed. The total number of therapeutic agents discussed was $N = 29$, of which $n = 7/29$ and $n = 6/29$ belonged to infectious diseases (ID) and oncology, respectively. The total number of purposes of these applications was $N = 46$, of which $n = 35/46$ (76%) were to seek permission to conduct a CT, and $n = 31/35$ (88.6%) were found registered with CTRI as on April 01, 2019. Of the $N = 46$ purposes, $n = 33/46$ (71.7%) were approved. Of the $n = 29$ INDs discussed, $n = 19/29$ (65.52%) were of the Indian origin.

**Conclusions:** Although a majority (65%) of INDs discussed in the meetings were of the Indian origin, the drug discovery was not in line to tackle the top ten causes of years of life lost prematurely (barring ID).

**Keywords:** Clinical trials, drug development, drug discovery, investigational new drug committee, investigational new drugs

**Address for correspondence:** Dr. Nithya J. Gogtay, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai - 400 012, Maharashtra, India.
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## INTRODUCTION

An Investigational New Drug (IND) is defined by the New Drugs and Clinical Trials (CTs) Rules (2019),[1] as "a new chemical/biological entity/substance that has not been approved for the marketing as a drug in any country." The IND Committee was set up under the Central Drugs and Standard Control Organization (CDSCO), Ministry of Health and Family Welfare (MOHW), Government of India in January 2001 (Right to Information reference number CDSCO/R/2019/50114, copy available on file) to advise the Drug Controller General of India (DCGI) on matters pertaining to CTs of IND for clinical development. This committee was reconstituted in August 2008 and subsequently in May 2009 with new members. The IND

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committee has been functioning, until recently, based on the Drugs and Cosmetics Rules, 1945, and now by the New Drugs and CTs Rules on March 19, 2019. The IND committee is chaired by the Director General of the Indian Council of Medical Research, New Delhi/Secretary, Department of Health Research, MOHW, Government of India. The committee comprises a core panel who are subject experts. These experts evaluate proposals seeking approval to conduct CTs on INDs for the scientific merit, regulatory compliance, and ethical standards. It is based on the recommendations from this committee that the DCGI issues approval to conduct CTs for INDs. There is no separate policy or guideline that explains the structure and functioning of the IND committee in the public domain. Hence, an audit of the minutes of the IND committee meetings would help to understand the areas of drug discovery and clinical development in our country, and this was the study objective.

## METHODS

### Ethics

The study protocol was submitted to the Institutional Ethics Committee (EC/OA-56/2019) who accorded an "exemption from review" status, as the data were available in the public domain.

### Study design, selection criteria, and study sample

All the minutes of the IND committee meetings available in the public domain in the website of CDSCO (https://cdsco.gov.in/opencms/opencms/en/Committees/IND/) were included in the analysis. This constituted minutes of meetings conducted during the period January 2017–December 2018. Agenda items, which were postponed, were excluded from the study. Thus, data from the minutes of $N = 7$ IND committee meetings formed the study sample.

### Quality check

The minutes of the meetings were independently reviewed by two authors, and any discrepancies or disputes were adjudicated by the senior author.

### Data extraction

The agenda items were classified as (a) initial application and (b) a repeat application. Some agenda items had more than one purpose, and hence, the total number of purposes of applications was calculated. These items were then analyzed to identify the various INDs being discussed and their respective therapeutic areas. The purposes were further classified as to whether they were applications seeking (a) approval to conduct a CT, (b) an amendment, and (c) a report submission. The applications seeking approval to conduct a CT were further classified based on the phase of the CT for which approval was sought. The status of registration of the IND with the CTs Registry of India (CTRI) was checked from the CTRI website (http://ctri.nic.in/Clinicaltrials/login.php). The outcomes of each of the purposes of applications were summarized as either accepted, rejected, or further clarification sought. We evaluated the country of the inventors as registered in the patent application, and this was identified as the country of development of the IND. This was done by searching patents in the websites of United States Patent and Trademark (https://www.uspto.gov/) and Google Patents (https://patents.google.com/).

### Outcome measures

Primary – Therapeutic areas of INDs discussed and the purposes of the applications. Secondary – The phase of CT, the status of registration with the CTRI, the outcomes of the applications, and the country of the invention of the IND.

### Data management and statistical analysis plan

Microsoft Excel (Publisher: Microsoft Corporation, Redmond, Washington, USA, 2016) was used for the analysis. Descriptive statistics using frequency and percentages were used to depict data.

## RESULTS

### Demographics

The total number of agenda items listed in the minutes of the seven IND committee meetings held during the 2-year period was $N = 45$. However, one agenda item was excluded as it was postponed, and hence, $n = 44$ items were finally analyzed. Of these, $n = 17/44$ (38.6%) were initial applications, and the remaining (27/44 [61.36%]) were repeat applications.

### Investigational New Drugs discussed and their therapeutic areas

The total number of INDs discussed in these meetings was $N = 29$, of which $n = 8/29$ (27.59%) were biologics and the rest $n = 21/29$ (72.41%) were New Chemical Entities (NCEs). The most common therapeutic areas of the drug development were infectious diseases (ID) and oncology with $n = 7/29$ (24.14%) and $n = 6/29$ (20.69%) INDs, respectively, being evaluated. The details of the other therapeutic areas are depicted in Table 1.

### The purposes of applications

Of the $N = 44$ agenda items, two items had two purposes each. Thus, the total number of purposes was $N = 46$. Of these, $n = 35/46$ (76%) were applications seeking approval to conduct a CT, $n = 5/46$ (11%) were applications seeking

**Table 1: Therapeutic areas of Investigational New Drugs discussed over the past 2-year period (*n*=29)**

| Therapeutic area | Frequency, *n* (%) | Molecules under development (indication) |
|---|---|---|
| Infectious disease | 7 (24.14) | Chikungunya vaccine, Zika vaccine, rabies monoclonal antibody, FDC of arterolane + piperaquine (malaria), levonadifloxacin - quinolone, nafithromycin - macrolide and HRF-4467 - HIV maturation inhibitor |
| Oncology | 6 (20.69) | PNB-028 (colon and pancreatic cancers), NRC-2694-A (head-and-neck squamous cell carcinoma), bioplatin (solid tumors), K0706 (leukemia), picropodophyllin (solid tumors), apaziquone (oral leukoplakia) |
| Diabetes mellitus | 4 (13.79) | CPL-2009-0031, saroglitazar, remogliflozin, PBL-1427 |
| Hematinics and cardiovascular diseases | 3 (10.34) | Desidustat (anemia in chronic kidney disease), TRC-041266 (congestive heart failure), PMZ-2010 (shock) |
| Pain | 2 (6.90) | Tapentadol, ZYKR1 |
| Contraception | 2 (6.90) | RISUG (male contraceptive), human chorionic gonadotropin β-LTB vaccine |
| Dermatology | 1 (3.45) | FDC of HT61 HCl 0.75% w/w + mupirocin 1.0% w/w + neomycin sulfate 0.5% |
| Psychiatry | 1 (3.45) | Endoxifen (bipolar affective disorder) |
| Orthopedics | 1 (3.45) | GRC-27864 (osteoarthritis) |
| Neurology | 1 (3.45) | PMZ-1620 (Alzheimer's dementia) |
| Genetic disorders | 1 (3.45) | Arimoclomol (Gaucher's and Niemann–Pick's disease) |

FDC=Fixed dose combination, HIV=Human immunodeficiency virus, RISUG=Reversible inhibition of sperm under guidance, β-LTB=B subunit of heat-labile enterotoxin of escherichia coli, HCl=Hydrogen chloride

permission to amend an already approved the study protocol, and *n* = 6/46 (13%) were report submissions.

### Phase of clinical trials and their Clinical Trials Registry of India registration status

Of the *n* = 35/46 (76%) applications that sought approval to conduct a CT, *n* = 12/35 (34%) each, were Phase I and Phase III CTs; whereas, *n* = 8/35 (23%) and *n* = 3/35 (9%) were Phase II CT and Phase I/II CT, respectively. CTRI registration had been done for *n* = 31/35 (88.6%) of the CTs as on April 01, 2019.

### Outcomes of the applications

Applications which included report submission and amendments were all approved. However, only *n* = 22/35 (62.86%) applications seeking approval to conduct a CT were approved. The remaining *n* = 4/35 (11.43%) applications were rejected with an advice to re-apply, and *n* = 9/35 (25.71%) applications required further clarification.

### Country of Invention of the Investigational New Drugs

Of the *n* = 29 INDs, *n* = 19/29 (65.52%) were from India and *n* = 4/29 (13.79%) from the USA. There was one IND which was jointly developed in Germany and Malaysia and one each from Sweden, Japan, and Germany. We were unable to find out the country of the invention of *n* = 2/29 (6.9%) INDs.

## DISCUSSION

This study found that the total number of IND committee meetings conducted over a 2-year period was *N* = 7, and the number of INDs discussed in these meetings was *n* = 29. The most common areas of the drug development were ID followed by oncology, and 62.9% of applications seeking approval to conduct a CT were approved. Nearly 65% of all INDs were of the Indian origin.

India is the second largest country in the world in terms of population next only to China, the metrics related to INDs could be considered very low. In China, there were 89 IND applications for NCEs (Class 1 drugs) in the year 2016; 143 in 2017 and 132 by the end of November 2018.[2] In China, a Class I new drug is defined as "NCEs that have never been marketed anywhere in the world."[3] The situation in Japan too is very similar to China. The number of initial CT notifications of NCEs in Japan was 119 in the year 2009 and 121 in 2010.[4] Thus, we may infer that there are limited research and development (R and D) in our country which would explain the limited functioning of the IND committee.

Based on the data available from the Institute of Health Metrics and Evaluation, the top ten causes of years of life lost (YLL) prematurely in India in the year 2017 are ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), stroke, diarrheal disease, lower respiratory tract infectious diseases, tuberculosis, neonatal disorders, asthma, diabetes mellitus, and chronic kidney disease.[5] Malignancies do not feature in the top ten causes of mortality in India, but it is one of the most common therapeutic areas of the drug development in our country. The fact that drugs for IHD, COPD, and stroke are not the major areas of drug development in India which indicates that drug development is not completely in-line with the country's needs although the listing of ID is encouraging. These findings are in-line with those reported by Chaturvedi *et al*. who audited *n* = 3325 CTs registered with the CTRI from India between July 20, 2007, and December 31, 2015, and found that 16.4% of CTs were in the area of cancer, followed by diabetes (12.1%) and cardiovascular diseases (10.1%).[6]

Globally, there is a severe decline in drug development for IHD, COPD, and other cardiovascular diseases due to the

huge amount of data that needs to be generated before approval.[7] Second, in countries such as India, the increase in deaths due to diseases such as IHD, COPD, and other cardiovascular diseases is not purely due to them being unmet medical needs because of poor health-care systems coverage in all areas of the nation.[8] This may be true for some of the other therapeutic areas also. Thus, oncology though not mentioned in the top ten causes of YLL prematurely in India, it could still be considered an unmet medical need, for which R and D need to be carried out.

Although 65% of all INDs discussed in the meetings were from India, the R and D here is not completely in-line with the country's needs. This is because many Indian companies also serve a global market where the profit margins are higher and the needs of the developed nations are different, where malignancies and lifestyle diseases are common.[9] Furthermore, the drug pricing policies of the Indian Government to make it affordable, further discourages R and D to be in accordance to the needs of our country because of the low profit margin.[10] The indigenous innovator companies on the other hand face a stiff competition from the generic industry,[10] thereby dissuading them from investing in R and D relevant to the country's needs. Differding[11] states in his review that out of the top 100 leading (by revenue) pharmaceutical and biotechnology companies in India, only 28 have contributed to the R and D between 1994 and 2016 with a mere 168 small molecule proprietary drugs (excluding biologics, botanicals, herbal extracts, fixed dose combinations of existing drugs, and repositioned existing products) being discovered. Further, India lacks infrastructure and technical skills in the drug development which is vital for pharmaceutical R and D.[12]

Our study is limited by a 2-year evaluation, as the minutes of the meetings conducted before the year 2017 were not available in public domain precluding a trend analysis. Our finding with regards to the R and D environment in India may be skewed as Indian R and D companies may not be bringing their Phase I study applications due to the nonavailability of regular and periodic IND committee meetings. This, in turn, could delay the entire regulatory approval process, thus dissuading the Indian companies from doing early phase CTs in India. On the other hand, IND meetings are set up only when there are adequate proposals to discuss. Hence, the IND committee does not have a calendar of meetings in the public domain which the companies may perceive it as a hurdle to plan their submissions.

## CONCLUSIONS

We find that the total number of meetings and the agenda items was very few, indicating a slow-paced drug development in our country. Although a majority (76%) of the agenda items evaluated were applications seeking approval for the conduct of CTs, the total number of applications on the whole was less when compared with China or Japan. It is encouraging to see that approximately 65% of INDs discussed in the meetings during the years 2017 and 2018 were of the Indian origin, but they were not completely in-line with the country's needs to tackle the top ten causes of YLL.

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### Conflicts of interest
There are no conflicts of interest.

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