Original Article

An audit of minutes of Subject Expert Committee meetings as a metric to assess the clinical research roadmap of India

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Abstract

Background: In January 2015, the Drugs Controller General of India approved the formation of 25 Subject Expert Committees [SEC] to aid the office of the Central Drugs Standard Control Organization [CDSCO] with regards to decision making. The present study is an audit of the minutes of the meetings the SECs held over the past three years.

Methods: All minutes during the period 1st July 2014 to 31st October 2017 were accessed from the CDSCO website. Applications were classified as those for clinical trials [CT] and those for marketing authorization [MA]. Each application was classified as being approved, amendment requested for or rejected.

Results: A total of $n = 317$ meetings were held over a 40 month period with $n = 2616$ agenda items. The Oncology/Hematology SEC had the maximum number of meetings at n = 48 [15.1%]. Only $n = 2030$ [77.6%] were evaluable agenda items. There were 1082 [53%] applications for clinical trials, and 948 [47%] applications for MA with or without a request for a clinical trial waiver[CTW]. Applicants seeking CTW were 5 times more likely to be rejected [for the waiver] relative to those not seeking waivers (cOR 5 [3.8, 7], $P < 0.001$). CTW applications for Oncology were 6.5 times more likely to be granted a waiver (cOR 6.5 [3.5, 11.7], $P < 0.001$). Considerable variability was seen in the minutes.

Conclusion: A vast majority of CT applications in the country receive approval, as do a majority of marketing authorization applications. Oncology, vaccine and opthalmology division predominate the approvals. There exists considerable heterogeneity in the minutes. Standardization of these minutes across committees will help add to the existing transparency and give greater insights into the decision-making process.

Keywords: CDSCO, Regulatory decision-making, Clinical Trials, Drug Approvals

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INTRODUCTION

On January 5, 2015, the Drugs Controller General of India (DCGI) approved the constitution of 25 panels of subject experts from various therapeutic areas to assist the Central Standard Drugs Control Organization (CDSCO) in the evaluation of applications for clinical trials (CTs) and market authorization of new drugs and new medical devices.[1] The idea behind their creation was to aid the office of the DCGI in decision-making through an evaluation of preclinical data, and clinical development data [Phase I-IV trials] of new drugs, biologics, and devices. In addition, the Subject Expert Committees (SECs) would also debate on global CTs[GCTs], biologics and products derived from

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recombinant DNA technology, fixed-dose combinations of two or more drugs, matters pertaining to drug safety as also defining a roadmap for the clinical research industry. While considering the approval of GCTs, the SECs factor in unmet medical need, is it an innovation over existing therapeutic options and a careful risk-benefit assessment. Similarly, if a company applies for marketing authorization (MA) with a CT waiver (CTW), the SEC considers whether there is a national emergency, extreme urgency, a national epidemic, the drug is an orphan drug for rare diseases or drugs indicated for conditions for which there is no existing therapy.

The Technical Committee reviews the recommendations of the SECs, and the latter's recommendations form the basis of the decision-making by the CDSCO. The SECs were formerly called the New Drugs Advisory Committee, and the name change was effected after the Dr. Ranjit Roy Chaudhury Committee recommendations.[2] The setting up of these committees has invited its fair share of criticism ranging from delays in decision-making to the choice of experts serving on these committees.[3]

Against this backdrop and given that it is close to 3 years since the setting up of SECs, the present audit was planned with the primary objective of evaluating the minutes of the meetings of SECs held over the past 3 years to give an insight into the functioning of these committees.

METHODS

Ethics

The study protocol was submitted to the Institutional Ethics Committee who deemed it exempt from review as the data were available in the public domain.

Study design, selection criteria and study sample

An audit was conducted of all the minutes available during July 1, 2014–October 31, 2017, on the CDSCO website.[4] Data from minutes of $n = 16$ SECs formed the study sample.

Quality check

Minutes were individually reviewed by each author. Any disputes or discrepancies were resolved through consensus.

Classification of the applications

Binary classification of the applications was made as those for CTs and those for MA. The former were further classified as those from Indian companies, those from companies headquartered outside India (MNCs), academic studies and those submitted by Contract Research Organizations (CROs). MA was sub-classified as CTW sought or not sought and then further into those from MNCs, Indian companies and those submitted by CROs.

Outcome measures

Each application was classified as being approved, amendment requested for or rejected.

Statistical analysis

Both descriptive and inferential statistics were applied to the data. Quantitative data were expressed as median (range) and categorical data as proportions. The association between CTWs sought (or not sought), and the decision to approve or disapprove the waiver was analyzed using the Chi-square test and a crude odds ratio with 95% confidence interval (CI) generated. All analyses were performed with 5% significance using Microsoft Excel. A qualitative synthesis of the minutes was also done.

Table 1: Distribution of meetings and agenda items among Subject Expert Committees

Serial number	Name of SEC	Total number of meetings	Total evaluable agenda items included (n=2030)		
			CT applications	MA applications without CTW	MA applications with CTW
1	Rheumatology/analgesics	22	96	51	17
2	Antimicrobial and antiviral	28	61	75	22
3	Cardiology/renal	29	132	54	24
4	Dentistry	1	0	0	2
5	Dermatology/allergy	21	42	35	34
6	Endocrinology	31	122	61	26
7	Gastroebterology/Hepatology	20	73	30	23
8	Nephrology	01	7	0	0
9	Neurology and psychiatry	20	65	42	18
10	Oncology and hematology	48	196	111	71
11	Ophthalmology	17	41	26	14
12	Orthopedics	8	2	21	3
13	Pulmonology	19	78	18	10
14	Radio diagnostics	5	3	6	3
15	Reproductive and urology	21	62	33	26
16	Vaccines	26	102	74	18
Total		317	1082	637	311

CT=Clinical trials, MA=Marketing authorization, CTW=Clinical trial waiver, SEC=Subject Expert Committees

RESULTS

Demographics

A total of *n* = 317 meetings of SEC were held over a 40 month period, with *n* = 2616 agenda items. The oncology/hematology SEC had the maximum number of meetings at *n* = 48, while dentistry and nephrology had the least at *n* = 1 (each). The total number of agenda items ranged from a minimum of 1 for the radiodiagnostics SEC to *n* = 20 for the vaccine SEC with a median of 8 (1, 20). Table 1 gives the details of the meetings and demographics of the agenda items.

Analysis of agenda items (*n* = 2616)

Of the total agenda items, *n* = 2030/2616 (77.6%) were evaluable as we excluded *n* = 586/2616 (22.3%) as the applicant did not turn up in 383/2616 (14%), 174/2616 (6.6%) were miscellaneous (items on the agenda not relevant to CT or MA) and (27/2616) [1%] were inconclusive/withdrawn agenda items.

Types of applications (*n* = 2030)

Of the evaluable agenda items, *n* = 1082/2030 (53%) were applications for CTs, while *n* = 948/2030 (47%) were for MA. In the latter, *n* = 637/948 (67.1%) did not seek a waiver while *n* = 311/948 (32.8%) sought a waiver. The distribution of these applications among the 16 SECs is shown in Table 1.

Of the CT applications, *n* = 619/1082 (57%) were made by Indian companies, *n* = 242/1082 (23%) were made by MNCs, *n* = 165/1082 (15%) were made by CROs and *n* = 56/1082 (5%) by academicians. Among the MAs in which CTW was not sought had *n* = 457/637 (72%) applications from Indian companies, 169/637 (26%) from MNCs and only 11/637 (2%) from CROs. Those MA applications seeking CTW had *n* = 188/311 (60%) applications from Indian companies, 118/311 (38%) from MNCs and only 5/311 (2%) from CROs.

Analysis of decision-making

Clinical trial applications (n = 1082)

Of these, *n* = 710/1082 (65.6%) were approved, *n* = 286/1082 (26.4%) were asked to be amended, while *n* = 86/1082 (7.9%) were rejected. The maximum approvals were in the areas of ophthalmology (76%) and pulmonology (73%) followed by reproductive medicine (72.6%), vaccines (72.5%) and oncology (72%).

Marketing authorization with clinical trial waiver sought (n = 311)

Of these, *n* = 197/311 (63.3%) were not granted a waiver, *n* = 93/311 (30%) were granted a trial waiver while amendments were asked for in *n* = 21/311 (6.8%). The maximum approvals were in the area of hematology/oncology (59%), cardiac/renal (33%), and ophthalmology (29%).

Marketing authorization with clinical trial waiver not sought (n = 637)

Of these, *n* = 382/637 (59.9%) were approved, in *n* = 97/637 (15.2%) amendments were asked for and *n* = 158/637 (24.6%) were rejected. The maximum approvals were in the area of vaccines (82%), hematology/oncology (71%), and dermatology (71%).

The details of decision-making are presented in Table 2.

Association between waivers sought/not sought and approval/rejection

Applicants seeking a CTW were 5 times more likely to be rejected for the waiver relative to those not seeking waivers (cOR 5 [3.8, 7], *P* <0.001). When CTW sought was analyzed for Oncology (relative to all other SECs combined), CTW was 6.5 times more likely to be granted (cOR 6.5 [3.5, 11.7], *P* <0.001).

Qualitative analysis of minutes

The way the minutes were written varied between committees. Often, the name of the sponsor that was represented by the CRO was not listed. The names of the SEC members were not listed. In addition, for CT applications, the narrative on the protocol discussion among the SEC members [for example risk-benefit] was not detailed.

DISCUSSION

The present audit of *n* = 2030 agenda items from *n* = 317 meetings held over a 40 months showed that applications for CT and MA each constituted approximately half of the applications with considerable heterogeneity in decision-making.

Almost 60% of the CT applications were made by Indian companies indicating that a sizeable chunk of clinical research in the country is being done by the local pharmaceutical industry. Given that only a quarter of the applications came from industry outside the country, India is a relatively smaller contributor to GCTs. The 5% contribution to the CT applications by academicians is a likely reflection of the challenges they face in funding and conducting studies on their own without the backing of the pharmaceutical industry.

With regard to the *n* = 1082 applications for CTs and assuming that the quarter of the CT applications that

Table 2: Decision of Subject Expert Committees on clinical trials and marketing authorization applications

Serial number	Name of SEC	Clinical trials (*n*=1082)			MAs without CTW (*n*=637)			MAs with CTW (*n*=311)		
		Approved	Amendment	Rejected	Approved	Amendment	Rejected	Approved	Amendment	Rejected
1	Rheumatology/analgesics	57	34	5	24	13	14	1	2	14
2	Antimicrobial and antiviral	26	27	8	35	9	31	9	2	11
3	Cardiology/renal	85	37	10	32	9	13	8	1	15
4	Dentistry	0	0	0	0	0	0	0	0	2
5	Dermatology/allergy	24	15	3	25	8	2	1	2	31
6	Endocrinology	86	28	8	34	9	18	5	3	18
7	Gastroenterology/ hepatology	46	17	10	16	6	8	4	3	16
8	Nephrology	1	2	4	0	0	0	0	0	0
9	Neurology and psychiatry	35	24	6	21	9	12	4	1	13
10	Oncology and hematology	141	39	16	79	15	17	42	7	22
11	Ophthalmology	31	7	3	14	1	11	4	0	10
12	Orthopedics	1	1	0	10	4	7	0	0	3
13	Pulmonology	57	13	8	7	2	9	5	0	5
14	Radio diagnostics	1	2	0	1	0	5	0	0	3
15	Reproductive and urology	45	14	3	23	5	5	7	0	19
16	Vaccines	74	26	2	61	7	6	3	0	15
Total		710	286	86	382	97	158	93	21	197

MA=Marketing authorization, SEC=Subject Expert Committees, CTW=Clinical trial waiver

were asked to be amended were eventually approved, the data shows that almost 92% of CT applications do receive approval and it is a very small proportion that gets rejected. Chaturvedi *et al.* analyzed *n* = 3325 trials registered with the Clinical Trials (CTs) Registry of India between July 20, 2007 and December 31, 2015 and found that the largest number of trials were in the area of oncology (16.4%).[5] There were 70% or more approvals in the area of oncology with regard to both CTs and MAs with or without a request for a CTW, as seen by us, indicating that it is a predominant area of research in the country. In the past decade, there have been considerable changes in ocular drug delivery, improved understanding of the pathogenesis of ophthalmic diseases and the emergence of anti-angiogenic and neuroprotective drugs.[6] This is reflected in a large number of approvals in the area of Ophthalmology. Similarly, the large number of approvals in the area of vaccines is likely an indication of commitment to the global vaccine action plan endorsed by 194-member states of the World Health Assembly (including India) with the objective of preventing millions of deaths by 2020 through more equitable access to existing vaccines for which CTs are a forerunner.[7]

With regard to MAs either seeking or not seeking a CTW (*n* = 948), when we combined approvals and amendments in both groups (assuming that amendments were eventually approved), we found that 593/948 (63%) were approved indicating that two-thirds of MA applications did receive approval. Almost 64% of applications for MA seeking a CTW were disallowed. Given that the minutes of the meeting do not give the rationale for this decision, it is hard to surmise what may have actually transpired. While putting up the minutes of the SEC meetings by the Indian regulator is a significant step toward transparency, lack of details within minutes and the considerable variability in the minutes makes it difficult to get insights into the decision-making. In January 2017, a handbook for applicants and reviewers of CTs of new drugs in India was released by the CDSCO in collaboration with the Indian Council of Medical Research [ICMR].[8] It is hoped that this handbook will standardize and streamline both applications, the process of evaluation and subsequent decision-making.

The study is limited by the fact that we did not do a sub-group analysis of approvals/amendments/rejections between applicants (Indian companies, Multinationals and CROs). Furthermore, the audit had a limited time-frame that did not give an insight into trends regarding decision-making over a period.

CONCLUSION

Our audit of a little over 2000 applications to SECs showed that a vast majority of CT applications in the country do get approved, as do a majority of MA applications. Oncology, vaccine and ophthalmology divisions predominate the approvals, and there is considerable heterogeneity in the minutes with almost no insight into the process of decision-making. Standardization of these minutes across committees will help add to the existing transparency.

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Nil.

Conflicts of interest

Dr. Urmila Thatte serves on the Oncology Subject Expert Committee.

REFERENCES

1. Order Passed by Directorate General of Health Services, Ministry of Health & Family Welfare and Office of Drugs Controller General (India); 5 January, 2015. Available from: http://www.cdsco.nic.in/writereaddata/Subject%20Expert%20Committee%20%20Directorate%20order.pdf. [Last accessed on 2017 Dec 15].
2. Order Passed by Directorate General of Health Services, Ministry of Health & Family Welfare and Office of Drugs Controller General (India); 3 July, 2014. Available from: http://www.cdsco.nic.in/writereaddata/officer%20order%201.pdf. [Last accessed on 2017 Dec 15].
3. Ghooi RB. Expert committee to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs-comments. Perspect Clin Res 2014;5:100-7.
4. CDSCO Website: Available from: http://www.cdsco.nic.in/forms/Default.aspx. [Last accessed on 2017 Jan 01].
5. Chaturvedi M, Gogtay NJ, Thatte UM. Do clinical trials conducted in India match its healthcare needs? An audit of the clinical trials registry of India. Perspect Clin Res 2017;8:172-5.
6. Zhang K, Zhang L, Weinreb RN. Ophthalmic drug discovery: Novel targets and mechanisms for retinal diseases and glaucoma. Nat Rev Drug Discov 2012;11:541-59.
7. WHO's 'Global Vaccine Action Plan 2011-2020'. Available from: http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/. [Last accessed on 2017 Dec 28].
8. ICMR & CDSCO's 'Handbook for Applicants & Reviewers of Clinical Trials of New Drugs'; January 2017. Available from: http://www.cdsco.nic.in/writereaddata/Scan1.pdf. [Last accessed on 2017 Dec 28].