ORIGINAL RESEARCH

Impact of COVID-19 and New Clinical Trial Rules, 2019 on Clinical Trial Applications in India

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ABSTRACT

The central drugs standard control organization (CDSCO), Indian national regulatory authority under the Ministry of Health and Family Welfare have revised the clinical trial regulations in 2019 and there was a tremendous change in the approach for regulatory approvals due to the COVID-19 pandemic. A tremendous strain has been observed on the clinical research activities due to the COVID-19 pandemic which involves the redirection of resources and avoidance of personal meetings. Therefore, an urgent need of innovative solution was identified to enhance the overall performance clinical research during this pandemic. The innovative solutions include involvement of digital biomarkers, digital information consent form, digital health record and digital case report form. In the present study, impact of new drugs and clinical trials rules 2019 and COVID-19 pandemic on clinical trials applications received by CDSCO and evaluated by Subject Expert Committees (SEC) have been analyzed retrospectively. The author concluded that new drugs and clinical trials rules were enforced recently by the regulatory bodies to meet the requirement of emergency medical conditions. A large number of variations in the clinical trials application were observed in terms of the types of trial and the procedure after the implementation of new clinical trial rules.

Keywords: Clinical Trial Applications, COVID-19, New Drugs and Clinical Trials Rules (NDCT) 2019, Subject Experts Committee.

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INTRODUCTION

To introduce new pharmaceutical products in the market, India is one of the ideal locations for clinical trials and is a new choice of the innovator pharma industries due to its huge patient pool, highly skilled professionals, and variety of sites etc. Although, the Indian clinical market is growing rapidly but still have lot of potential as it currently holding 16% of total world's population and majority of world's disease burden but still only 2% clinical trials registered worldwide so far involves the limited populations and specific gender (preferably the male).[1] Now the scenario of the clinical trial in India seems improving with greater participation of women, but still there is limited participation of the children and the neonates. Despite the rapid growth of the pharmaceutical industry in India, clinical research is still lagging behind because of non-favorable public opinion as there are many companies which wish to conduct the trials without following any ethical and regulatory procedures. Because of poor media and inadequate regulatory bodies, the clinical trial in India came to a pause. When we look at the data registered for the clinical studies at the Clinical Trials Registry- India (CTRI), out of 7,232 clinical studies, 5,336 studies (74%) are classified as interventional trials. Among these interventional trials, only 2,522 (48%) studies involve the usage of allopathic drugs (2065, 39%); biologics (256, 5%) and vaccines (201, 4%). Remaining 52% studies include the interventions based on alternate system of medicines such as AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy), probiotics and medical devices. Out of 2,522 studies conducted for allopathic drugs, biologics, and vaccines, 901 studies (36%) are sponsored by the non-profit agencies followed by 864 studies (34%) sponsored by foreign/ global firms and remaining 728 studies (29%) are sponsored by Indian pharmaceutical firms.[1,2]

Out of the clinical studies conducted in India, about 66% are either phase III or phase IV trials and rest 34% are observational studies. The studies which are labeled as phase III are sponsored by both the foreign companies (53%) and the Indian companies (35%). These mostly represent trials of Investigational New

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Drugs (IND), New Chemical Entities (NCEs) or the Global Clinical Trials (GCTs). The remaining phase III and IV trials were mostly sponsored by non- profit agencies.[2]

Currently, the government of india introduced the New Drugs and Clinical Trial (NDCT) Rules, to replace part XA and schedule Y of the Drugs and Cosmetics Rules 1945. The new regulations shelter the facility for promoting clinical research with clear guidelines on some important topics such as clinical trials of orphan drug and pre- and post-submission meeting specially during pandemic. The new rules provide prospective measures to promote clinical research considering moral and quality standards. The approval system made in place in time bound manner to speed up the disposal of submitted application to CDSCO and encourage clinical research. New provisions have involved accelerating product approval during emergency situations, pre and post submission meetings with authorities may add increased certainty and assurance. The well-structured New Rules comprises of 13 chapters (including 107 rules), 8 schedules, and 27 forms with responsibility index of all stake holders.

Regulatory Structure of India for the Clinical Trials

As the pharmaceutical industry started growing, the need for the new and effective medical treatment had risen. Due to which the clinical trials came into its role on full swing in 1990s. The change occurred in 2012 when the female activists signed a petition on a vaccine to be tested on teenage girls in at supreme court clamming of the ethical delinquency happened in the trial.[3] CDSCO is the core and exclusive regulatory authority of India and the drugs controller general of india (DCGI) are deputed for providing the approval of clinical trials.[1,4] Along with this, one more apex body namely Indian Council of Medical Research (ICMR) is also responsible for the regulation, coordination and promotion of best practices related to the biomedical research.[5] In order to conduct the clinical trials in india, investigator must ensure the following rules

- Incompliance with an Ethical Committee (EC)and a DCGI approved protocol
- In the case of Investigator Initiated Trials (IITs) with new drugs, DCGI approval is no longer needed; only an EC approval is required as per G.S.R.313 (E) dated 16th March 2016.
- In compliance with GCP guidelines
- Registration of Ethical Committees (Rule 122DD): All the Institutional Ethical Committees (IECs) need to be registered with CDSCO and registration should be renewed at the end of three years.
- Approval from Institutional Ethics Committee: (i) In order to regulate the clinical trials, this is compulsory to have an approval from the IEC, (ii) A major change in the current guidelines are related to the academic trials. As per the new guidelines the DCGI approval is not mandatory for academic trials, instead the approval of IEC would be sufficient. (iii) In case of potential overlap between the regulatory and academic purposes of the clinical trials, the IEC will inform to the DCGI.

Procedure for Conduction of Clinical Trials in India

As per the NDCT, the following steps are to be taken for clinical trials in india:

Pre-submission Meetings

Under the provisions of NDCT Rules, 2019, if anyone wants to conduct pre-submission meetings related to manufacturing and imports of new drugs or want to conduct clinical trials, may requests through an application for a pre-submission meeting with CDSCO authority.

Permission to Conduct Clinical Trials in India (Rule 122DA)

As per the regulation, the application (Form CT-04) is to be submitting through online mode. The permission may be granted via Form CT-06 If all conditions are satisfactorily. The necessary documents specified under second schedule should be attached with the application along with the required fees mentioned in the sixth schedule of the NDCT Rules, 2019.[6,7] The application will be submitted online via the SUGAM portal which provides comprehensive step-by-step instructions.[6,7] Submitted application will be checked by SEC followed by Technical Committee (TC) and apex committee. Drug Controller General of India (DCGI) will grant approval for conduct of clinical trials after obtaining approval from all three stages. Also, it requires mandatory registration on Indian Council of Medical Research (ICMR) website. The validity of approval for clinical trials is only two years. CDSCO give the approval for further extension if requested by the investigator. CDSCO also responsible of marketing authorization of the application. All the applications submitted to CDSCO forwarded to subject expert committee for their opinion and recommendation. Subject expert Committee comprises of expert mainly physicians from Government and Public Institutions. CDSCO has formed different subject expert committee as per therapeutic indications i.e., oncology, endocrinology, dermatology, ophthalmology, gastroenterology, and others. Subject expert committee is only approving committee under CDSCO.

Committee for Evaluation of Application

As per the NDCT rules, after submission the application will be reviewed by three tiered regulatory bodies which includes (a) SEC, (b) TC, and (c) Apex Committee. The approvals of the independent ethics committees (IEC) or Institutional Review Boards (IRB) are also required with the application. The application will be approved if it is satisfying all the criteria.

METHODS

The methodology of clinical trial approval was well described by the CDSCO, however the frequent amendments lead to the confusion. Therefore, an urgent need was there to further regulate the approval guidelines with the aim to give a further boost to the clinical trial. As a result of implications, the New Drugs and Clinical Trial Rules, 2019 (NDCT rules) were implemented. Figure 1 describes the flow chart of the evaluation process of clinical trials in India.

In the present study, authors highlighted the clinical trials applications received by CDSCO and evaluated by SEC before (January 2017 to March 2019) and after (April 2019 to March 2020) implementation of NDCT 2019, and impact of COVID-19 on various clinical trials conducted are also evaluated and summarized.

Following four period datasets were evaluated.

1. Proposals discussed in SEC from January to December 2017
2. Proposals discussed in SEC from January 2018 to March 2019 (before NDCT2019)
3. Proposals discussed from April 2019 to March 2020 (after NDCT 2019 enforcement)
4. Proposals discussed from April 2020 to December2020 (postCOVID-19)
5. Proposals discussed from January to November 2021

The manuscript also covers the impact on the Clinical Trial proposals, BA/BE studies, the proposals ratio for marketing and manufacturing, subsequent new drugs proposals, change in the ratio of PK study proposals before and after implementation of New Clinical Trial Rules 2019. Manuscript also illustrated the significant increase in number of Clinical trial applications including alternative therapies, SND proposals, fixed drug combination, vaccine post COVID-19.

RESULTS AND DISCUSSION

Central Drugs Standard Control Organization is the apex body which regulates the conduct of clinical trial. CDSCO give the approval for the conduct of clinical trials in India along with the marketing authorization of the application. All the applications submitted to CDSCO forwarded to Subject Expert Committee for their opinion and recommendation. Subject expert committee comprises of expert mainly physicians from government and public Institutions. CDSCO has formed different subject expert committee as per therapeutic indications i.e., oncology, endocrinology, dermatology, ophthalmology, gastroenterology, and others. Subject expert committee is only approving committee under CDSCO.

Proposals Number, Types and Therapeutic Category deliberated in SEC: Pre-COVID

From Jan 2017 to Dec 2017, total 535 applications (Figure 2A) were deliberated in SEC meetings. However, before NDCT from January 2018 to March 2019, total 750 applications were deliberated in SEC meetings (Figure 2B). Nevertheless, after NDCT but before COVID, from April 2019 to March 2020, total 761 applications were deliberated in SEC meetings (Figure 2C). In all these three cases few applications were approved by SEC, some were rejected, and some are under further considerations. Category wise classification of applications submitted to SEC are shown in Figure 3. For the year January 2017 to December 2017 (Figure 3A), before NDCT (January 2018 to March 2019 – Figure 3B) and After NDCT (April 2019 to March 2020 – Figure 3C). All the applications received were categorized as under consideration, rejected and accepted. Figure 4 describes the applications received under these three types and their therapeutic use.

Proposals Number, Types and Therapeutic Category deliberated in SEC:Post-COVID

Recently, CDSCO has formed new Subject Expert Committee specific for Covid related cases. Usually, the frequency of SEC meeting is once in a month. However, considering the urgency and to expedite the approval of COVID related applications. The SEC for COVID related cases happened once in a week. During COVID pandemic, different types of applications were submitted to CDSCO mainly clinical trial application, academic study, import and marketing, manufacturing and marketing etc. All the applications were reviewed by CDSCO and forwarded to SEC for their opinion. During April to December 2020, total 170 applications were deliberated in SEC meetings as shown in Figure 5. By comparing clinical trial approval data from January 2017 to December 2020, we have observed a major change in the acceptance ratio by the CDSCO. During the years 2017, 2018, 2019 and 2020. It was 77, 72, 88, and 62.5% respectively showing any of the following possibilities.

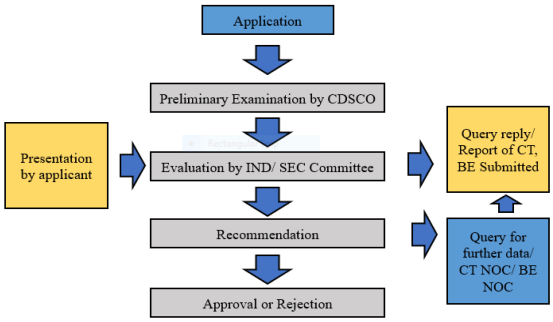

Figure 1:. Submission Committee Evaluation Process

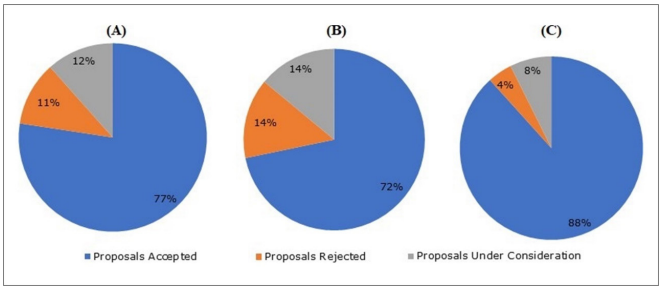

Figure 2: Proposals discussed in SEC (A) January 2017- December 2017; (B) January 2018 – March 2019; (C) April 2019 – Mar 2020

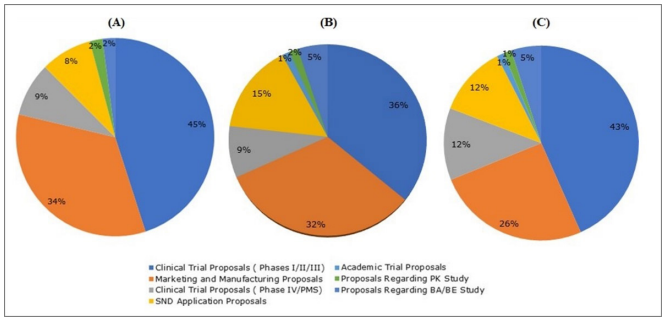

Figure 3: Category-wise classification of proposals submitted to SEC (A) Jan 2017- Dec 2017; (B) Jan 2018 – Mar 2019; (C) Apr 2019 – Mar 2020

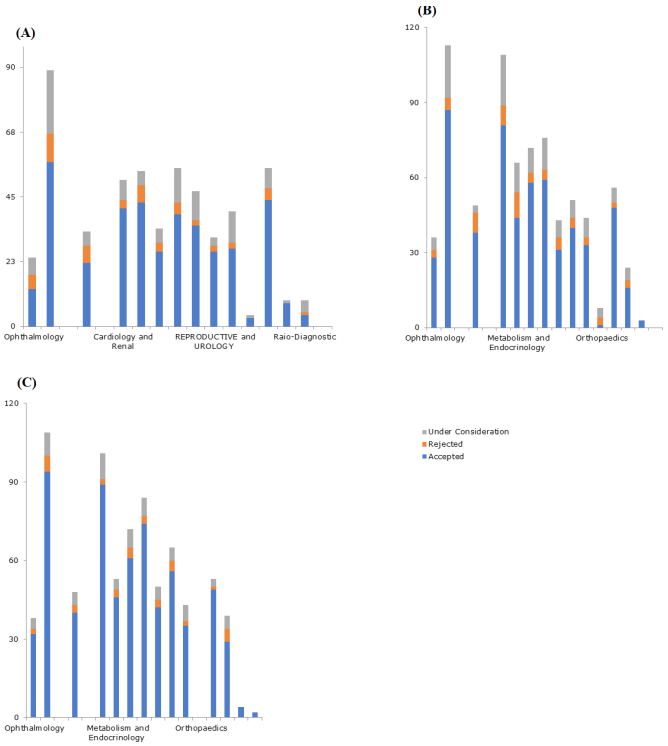

Figure 4: Therapeutic based classification of proposals submitted to SEC (A) Jan 2017- Dec 2017; (B) Jan 2018 – Mar 2019; (C) April 2019 – Mar 2020

- Due to the introduction of too many new COVID-19 trials, some of the applications did not have the preliminary testing done on the pre-clinical level making it difficult to accept to begin a clinical trial without enough evidence.
- More number of clinical trial applications at the time of COVID-19 might have caused delay in the processing due to physical factors such as lockdowns. That could also be the reason that in Figures 2 and 6, we see a difference in the 'underconsideration' ratio too.
- Different types of applications were submitted and deliberated in the SEC meetings, mainly clinical trial applications and marketing authorization application. The details are shown in Figure 7. By comparing category wise Clinical trial proposal data from years January 2017 to December 2020, we have observed the below changes (Figures 3 and 8):
- Proposals for clinical trials (Phase I/II/III) were 45, 32, 4%, and 62.35% in the year 2017, 2018, 2019 and 2020, respectively. Higher ratio of phase I to III clinical trials in 2020 as compared with the data from 2017 to 2019. This could be because many new applications were received for COVID-19 drugs.
- Not much change is observed in the phase IV and PMS studies proposals. As phase IV, and PMS clinical trials are mainly for marketed and well-known drugs, this had almost no impact due to COVID-19.
- There is a slight increase in the number of academic clinical trial proposals during 2020. The number of such proposals

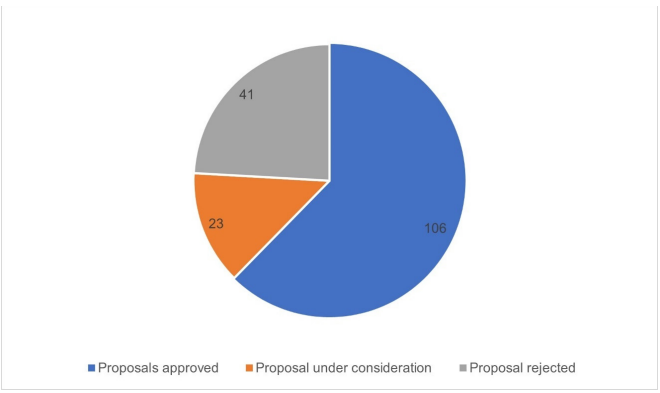

Figure 5: COVID-19 related proposal discussed during Apr 2020-Dec 2020

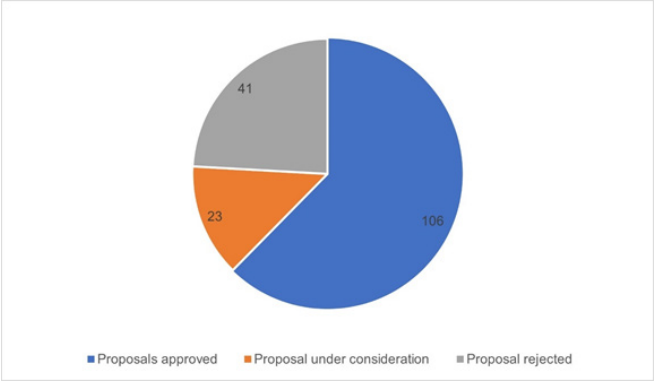

Figure 6: COVID-19 related proposal discussed during Apr 2020-Dec 2020 in percentage

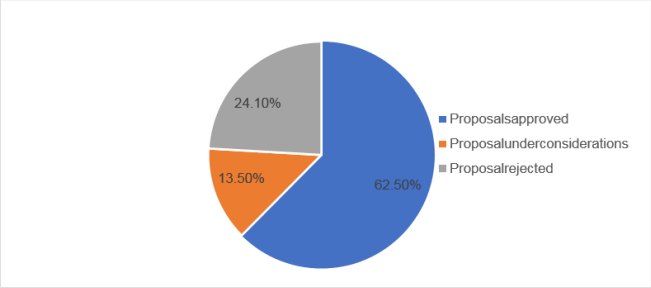

Figure 7: Types of COVID-19 related proposal discussed during April 2020 -Dec 2020

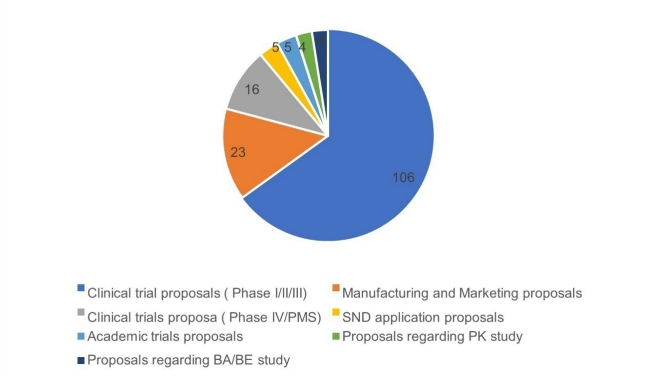

Figure 8: Types of COVID-19 related proposal discussed during Jan 2021- March 2021

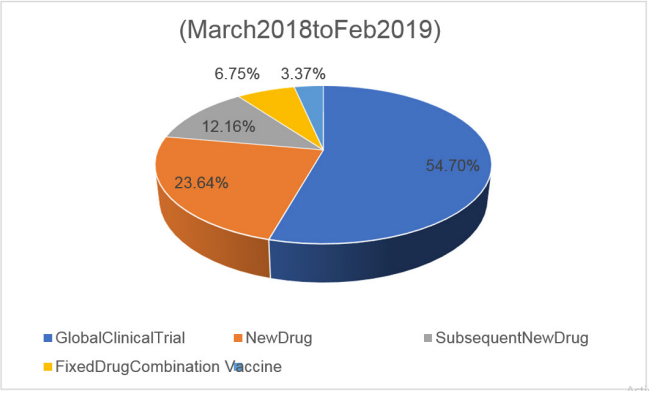

Figure 9: Percentage of clinical trials conducted data in March 2018–Feb 2019

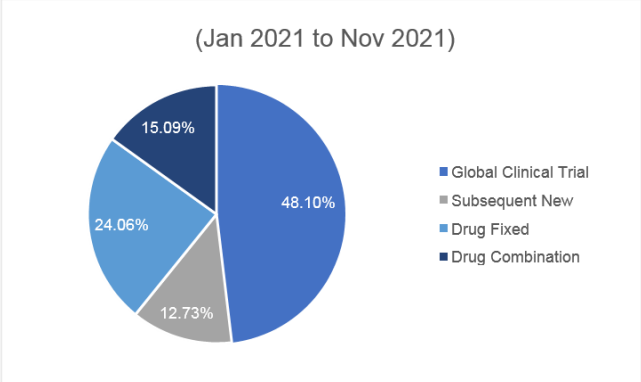

Figure 10: Percentage of clinical trials conducted in Jan 2021–Nov 2021

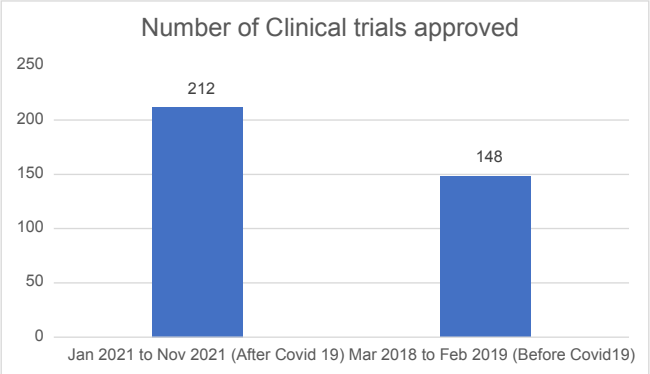

Figure 11: The Global clinical trials approval increases when compare between the March 2018 to Feb 2019 with Jan 2021 to Nov 2021

were 2, 1, 1, and 2.9% in the year 2017, 2018, 2019 and 2020 respectively.

- The percentage of BA/BE studies was slightly reduced in 2020 in comparison to 2018 and 2019. However, there is no such justification to understand the exact reason for this slight reduction.
- The proposals ratio for marketing and manufacturing reduced much during 2020 when compared to 2017 to 2019. It was 34, 32, 26, and 13.5% in years 2017, 2018, 2019 and 2020 respectively. This sudden change could be because of the manufacturing and marketing process affected due to COVID-19 much impacted by a number of unplanned lockdowns.
- The SND proposals were reduced during 2020 in comparison with 2017-2019. It was 8, 15, 12, and 2.9% in years 2017, 2018, 2019 and 2020 respectively.
- No considerable change in the ratio of PK study proposals was seen

Clinical Trial Approvals (Before and After COVID-19)

Considering March 2018 to February 2019 as a pre-COVID-19 time, and January 2021 to November 2021 as post-COVID-19 time, here is the overall comparative observations (Figures 9 and 10).

- Total number of clinical trial applications during pre-COVID-19 time were 148 in comparison to 212 in post-COVID-19 time. This clearly shows more demand and acceptance of new research and research methods. Also getting ready for much preventive approaches for building immunity. Unlike earlier, there were many applications even for the alternative therapies like Ayurveda, and Homeopathic medicines during post-COVID-19 time.
- Total reduction of 54.70 and 48.10% was observed in global clinical trial data during pre and post COVID-19 in 2021 in comparison of 2018 and 2019 respectively, This may be attributes due to the shifting of attention of many industries to COVID-19 treatment and most of the new applications were received for COVID-19 drugs.
- When comparing new drug percentage ratio in 2021 none of the clinical trial was granted for new drug.
- The Subsequent new drug proposals were slightly increases during 2021 in comparison with 2018-2019. It was 12.73 and 12.16%, respectively in years 2018-19 and 2019-20 respectively.
- Fixed drug combination related clinical trial approval increases in 2021 as compare with 2018 to 2019. These sudden changes may be due to development of new combination dosage forms and many were related to COVID-19 treatment.
- If comparing pre and post COVID-19 the vaccine related applications, there was increase in the vaccine clinical trial applications in 2021 as compare with 2018 to 2019 which may be due to awareness of vaccines as a preventive measure for COVID-19.

Also, if we are comparing of approval of the clinical trials with 2018 and 2021 there was increase in the number of approved trials as described in Figure 11. This might be due to more requirement COVID-19 treatment. Overall, post NDCT rules and impact of COVID-19 approach of pharmaceutical industry for carrying out clinical trials in India has been increased and it may be due to following changes and amendments in the NDCT rules by CDSCO.

The Major Changes in the New Rules 2019 were following [8]:

Here we are highlighting the major changes in the NDCT

(a) The application for the approval of clinical trial is required to be submitted to the authority via SUGAM which is an online portal hosted and managed by the CDSCO.

(b) In order to make the time efficient approval procedure, the time required for complete approval has been reduced to 30 days and 90 days for domestic and international manufacturer respectively.
(c) The provision for the medical management of any injury related to the trials has been more clearly defined.
(d) In case of permanent disability or death the DCGI will decide the compensation to the participants of related clinical trials. In case of adverse event the ethical committee will monitor the trials and decide on the amount of compensation. A special methodology for the calculation of quantum of compensation has been involved in NDCT rules.
(e) If the new drug which is already been approved and marketed in any of the countries specified by the DCGI, requirement of a local clinical trial may be waived for approval of this new drug.
(f) NDCT rules provides relaxation in the requirements of clinical trial Phase IV specicifically for those pharmaceuticals used for life-threatening condition or of special relevance, It also provide relaxation for the drug used in rare disease
(g) If any drug is approved in other country and already in the market from last two year, there is provision for requirement relaxation during animal toxicology studies, teratogenic studies, perinatal studies, mutagenicity, and carcinogenicity studies. Additionally, no permission is required from the CLA for conducting an academic clinical trial.
(h) There is a provision of increment in the application fees for conducting phase I to phase IV trials.
(i) The Phase IV study would include studies related to drug-drug interactions, dose response or safety studies, trials designed to support use under the approved indications.
(j) As per the NDCT rules, the free access of investigational products is to be provided by the sponsor to the participant after the completion of the clinical trial.
(k) This also involves the clear guidelines about the requirements for carrying out post-marketing surveillance studies (PMS). It is required to submit the periodic safety update reports (PSUR) at every six months for the first two years after the approval.
(l) For the application of drug used for pediatric and geriatric populations, the trial will be run on pediatric and geriatric participants.

CONCLUSION

COVID-19 has brought the various challenges not only in the pharmaceutical product developments but event at the front of regulatory bodies. New drugs and clinical trials rules were enforced recently by the regulatory bodies to meet the requirement of emergency medical condition. Numerous changes were observed in the clinical trial patter conducted in india before and after the COVID-19 pandemic. Finally, this pandemic has introduced a large amount of awareness about the significance of clinical trials to prove the safety and efficacy of drug and vaccines.

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