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Review Article

Comparision of Clinical Trial Application Approval Process with different countries guidelines

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Abstract

Background: *Clinical trial is vital step in the development of new and safe medicine & in the improving medical treatment. Clinical trial explore how a treatment reacts in the human body and are designated to ensure a drug is treated and effective before by regulatory authority and made available for doctors. The clinical trial approval or submission is the dossier that includes all documentation pertaining to the conduct of clinical trial in [country] according to the regulation. The clinical trial application must undergo a review or evaluation before being granted authorisation to conduct the trial in [COUNTRY] by [NAME OF NATIONAL REGULATORY AUTHORITY]. Drug trial regulation systems differs among countries and at this stage full harmonisation of the processes among the different International Conference of Harmonization of technical requirements for registration of pharmaceutical product for human use (ICH) regions of the world.*

Methods: *In this study, a methodology based on research articles, research journals, countries legal website and scientific publications have provided a basis for detailed analysis of timelines for clinical trial review and approval of eight regulatory authorities. This research shows that the various timelines and requirements of clinical trial approval process. Clinical trial regulatory guidelines of India compared with European Union, Canada, China, US, UK and Kenya and Australia. Timelines of clinical trial approval process and its requirements in India were compared with other respective countries.*

Results: *This study specifies various regulatory guidelines and safety requirements for conduct and inspection of clinical trials. It is required to take grant permission from regulatory authority to conduct clinical trial. The regulatory environment in USFDA, Kenya and Canada becomes more stringent in terms of timelines of approval.*

The information regard to clinical trial application approval (CTA) obtained from the official website of different countries; those were used to compare timelines and requirements of clinical trial approval process in India with EU, US, UK, China, Canada, Kenya and Australia. The flowcharts were prepared to compare timelines & requirements of safety reporting in India with respective countries. Total eight

regulatory authorities were included in this study which shows the different timelines and requirements for clinical trial approval process.

Conclusions: *The regulatory guidelines in the clinical trials vary between countries. And it is important to take permission from regulatory authority before conducting clinical trial. Under the regulation, sponsor will be required to apply for authorisation to conduct clinical trial. There is different timelines and requirements of clinical trial application approval process for each regulatory body. This study methodology has enabled comparisons to be made both within agencies and between different authorities and has identified differences in the timelines that applications spend indifferent stages of the review.*

Keywords: *Regulatory authorities, Clinical trial approval process, Timelines and requirements of CTA.*

Introduction

Clinical trial is vital step in the development of new and safe medicine & in the improving medical treatment. Clinical trial explore how a treatment reacts in the human body and are designated to ensure a drug is treated and effective before by regulatory authority and made available for doctors. The clinical trial approval or submission is the dossier that includes all documentation pertaining to the conduct of clinical trial in [country] according to the regulation. The clinical trial application must undergo a review or evaluation before being granted authorisation to conduct the trial in [country] by [name of national regulatory authority]. Drug trial regulation systems differs among countries and at this stage full harmonisation of the processes among the different International Conference of Harmonization of technical requirements for registration of pharmaceutical product for human use (ICH) regions of the world. The regulatory body ensures compliances in various legal and regulatory aspects of the drug. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations. These regulatory guidelines used to regulate drug development process, licensing, registration, manufacturing, marketing and labelling of pharmaceutical products. The following few regulatory agencies like-

1. USFDA(US)
2. MHRA(UK)
3. TGA(Australia)
4. Health Canada(Canada)
5. EMA(European Union)
6. CFDA(China)
7. PPB(Kenya)

These are the few regulatory agencies and organization established in respective countries

Method

In this study, a methodology based on research articles, research journals, countries legal website and scientific publications have provided a basis for detailed analysis of timelines for clinical trial review and approval of eight regulatory authorities. This research shows that the various timelines and requirements of clinical trial approval process. Clinical trial regulatory guidelines of India compared with European Union, Canada, China, US, UK and Kenya and Australia. Timelines of clinical trial approval process and its requirements in India were compared with other respective countries.

Results

Timeline of Clinical Trial/ IND Review Process

According to study, the clinical trial application content (see Table 1) and the assessment are divided into two parts - Part I and Part II, which were assessed in parallel unless the application only contains Part I. These regulations were shown that a strict adherence to the maximum timelines allocated to each phase. But the regulation has restricted timeframe for review. Part II review assessed by EC. It shown that the timelines which results into an increase or decrease to the overall timelines compared to other country. These review timelines of ECs varies by institution.

For part I-

In India and EU Clinical Trial Application (CTA) review process, these shown the same time for first review i.e.45 working days. Canada required very less time i.e. only 7 days. UK, US, Kenya required same review time i.e. 30 calendar days of review. The review process of Australia involved two schemes which review the CTA - CTN Scheme and CTX Scheme. CTN scheme review the CTA on a weekly basis. CTX Scheme required 30-50 days of review period. China required maximum time for CTA review i.e.100-120 days and additional 2 months for imported drugs.

India (Timeline of CTA review- within 45 working days)

India = EU (within 45 working days)

India > Canada (within 7 days)

India< China (As soon as possible)

India< Australia (within 30 or 50 days/ on a weekly basis)

India > US = UK = Kenya (within 30 days)

For part II-

India required 4 to 8 weeks for part II review. Review process of EU requires 76 Days + 50 days for advanced therapies or biologics. EU required maximum time after India for CTA approval. Whereas, UK required 60 calendar days for CTA review. The CTA review timelines in Canada, China, Australia and Kenya varies by institution.

India (Timeline of CTA review- required 4 to 8 weeks)

India >EU (76 Days + 50 days for advanced therapies or biologics)

India >UK (60 calendar days)

India > Canada = China = Australia = Kenya (timelines varies by institution)

India>US(Maintains its own review procedures and processes for review. No statement on review time)

Total review timelines required for CTA review

As per, Table no.(1) CTA review timelines shown that, CTA review process is done by two times, Part I review and Part II review. The total time required for the CTA review in India is 8 to 12 weeks. The total timerequired by China is within 155 to 195 days. China required maximum time as compared to other countries timelines.UK also required maximum time after China i.e. (90 days, or 180 days if a specialist group or committee is consulted). EU required [60 to 106(+50) days] for review of CTA. The total time for the CTA review in Canada and Kenya are same i.e. 30 days. Australia required 50 days for the CTA review.

India required total time for CTA review was 8 to 12 weeks

India < EU [60 to 106(+50) days]

India > Canada (30 days default review period commenced on the date of receipt)

India < China (within 155 to 195 days)

India < UK (90 days, or 180 days if a specialist group or committee is consulted)

India > Kenya (within 30 days)

India >Australia (within 50days)

India >US (within 30days)

Requirements for submission of CTA

According to the study, CTA approval process required following requirements.

Parallel regulatory and ethical review

Parallel regulatory and ethical review is permitted in India, EU, Canada, Australia, US and UK. The information about parallel regulatory and ethical review in China is not specified. Parallel regulatory and ethical review is permitted in Kenya.

Clinical trial application language

Most of the countries used English language for submission of clinical trial application. English language is required for submission of all applications and supporting data in India, EU, and Canada, Australia, US and UK. But in Canada French language also used as CTA language for registration & submission. There is no information about CTA language in Kenya.

Regulatory Fees

The regulatory authority of India, EU, China, UK and Kenya required fees for review of CTA. No regulatory fees required in Canada and UK for clinical trial application review.

Assembly and Number of Copies

The regulatory authority of India, Canada, and China required 4 copies [two (2) hard copies and two (2) soft copies (i.e., CDs in PDF format)] for CTA submission. UK required 3 copies of CTA. The regulatory authority of EU, Australia, US required 2 copies of CTA in both electronic and paper format.

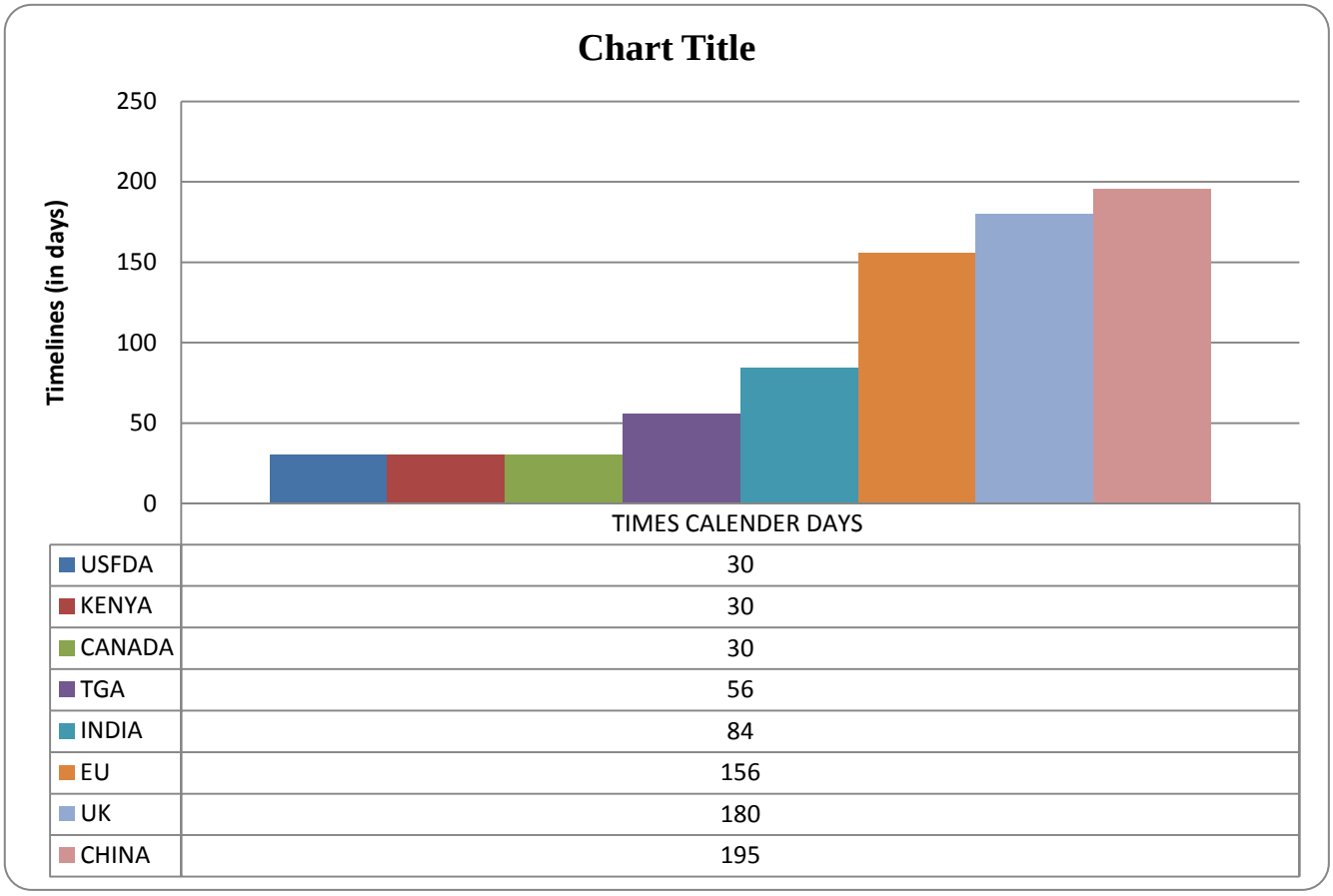
Table 1: Clinical Trial Application Review Timelines

S.N.	Country Name	Clinical Trial Application Review Timeline		Total
		Part I(regulatory review)	Part II(IEC review)	
1.	India (DCGI)	within 45 working days	Four (4) to eight (8) weeks.	8 to 12 weeks
2.	EU (EMA)	45- Days	76 Days + 50 days for advanced therapies or biologics	60-106(+50)
3.	Canada (HC)	7 days	timeline varies by institution	30 days default review period commenced on the date of receipt.
4.	China (CFDA)	100-120 days(additional 2 months for imported drugs)	As soon as possible	155 to 195 days
5.	Australia (TGA)	a. CTN Scheme - on a weekly basis b. CTX Scheme-30 or 50-days review period depending on the level of review (TGA + 20 days)	timeline varies by institution (earlier notification)	50 days
6.	US (FDA)	within 30 calendar days of receipt of the original IND	Maintains its own procedures and processes for review. No statement	30days
7.	UK (MHRA)	MHRA within 30 days	within 60 calendar days	90 days, or 180 days if a specialist group or committee is consulted
8.	Kenya (PPB)	PPB within 30 days of receiving a valid application	timeline varies by institution(earlier notification)	30 days

Table 2:

S.N.	Regulatory Authorities	Parallel regulatory and ethical review permitted(Yes/No)	Clinical trial application language	Regulatory Fees	Assembly and Number of Copies
1.	India (DCGI)	Yes	English	Required	4 copies
2.	EU (EMA)	Yes	English	Required	2 copies
3.	Canada (HC)	Yes	English or French	Not required	4 copies
4.	China(CFDA)	Unspecified	Standard Chinese	Required	4 copies
5.	Australia(TGA)	Yes	English	Required	2 copies
6.	US(FDA)	Yes	English	Not required	2 copies
7.	UK(MHRA)	Yes	English	Required	3 copies
8.	Kenya(PPB)	No	Unspecified	Required	2 copies

Figure 1:



Discussion

Timeline of Clinical Trial/ IND Review Process

The Comparisons between U.S. and European processes for the drug approval are similar, but 2 issues have elicited particular scrutiny: the time required for drug approvals and transparency of no published drug trials data.

For drugs, most of that time, in both Europe and the United States, is spent in clinical trials that can consume years and generate costs in the millions or even billions of dollars (table:01). Some proposals in Europe have called for earlier market release of drugs once they have completed Phase II clinical trials, with post-market surveillance thereafter to continually assess patient safety and drug efficacy.

Another determination of the concept to market period is the time it takes the regulatory agencies to conduct their reviews. It is commonly asserted that FDA processes are significantly slower than those of the EMA. Closer examination shows that, in fact, drug review times are significantly shorter than FDA followed by the EMA (table: 01). One study demonstrated that for similar drugs, the median times of initial reviews were 303 and 366 days, respectively, and for full reviews was 322 days compared with 366 days, respectively. Comparing first-to-market times between the United States and Canada, 85.7% of drugs were available first in the United States, and a median of 355 days sooner. All of the drugs that were approved by both the FDA and EMA were available sooner to patients in the United States, in part because of consistently shorter review times of FDA.

Regulatory authorities include dealing with differing (and possibly opposing) regulatory requirements, including differing primary and secondary endpoint requirements, divergence in the requirements for the control arm, in clinical studies EU verses US verses Asia, obtaining agreement from differing health authorities. The level of evidence needed, based on the studies and based on the health authority resources.

Table: 01 showed that, TGA and EMA had fewer out-liers, and the difference between the fastest and slowest approval was far less than for the other agencies. This could be interpreted as showing the impact of the rigorously applied time limits for reaching a decision in the

Conclusion

The regulatory guidelines in the clinical trials vary between countries. And it is important to take permission from regulatory authority before conducting clinical trial. Under the regulation, sponsor will be required to apply for authorisation to conduct clinical trial. There is different timelines and requirements of clinical trial application approval process for each regulatory body. This study methodology has enabled comparisons to be made both within agencies and between different authorities and has identified differences in the timelines that applications spend indifferent stages of the review.

If once the amendment changes are clear from DCGI, hopefully the Indian clinical research industry booms up. There would be a drastic change in Indian clinical research market in future if all these considerations are well set with greater security, trust and technology.

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References

1. European Commission Memo, Brussels, 2 April 2014.
2. Guidelines for Review/Evaluation of Clinical Trials of Vaccines and Biologicals.
3. Understanding clinical trial booklet. GPS public affairs. 2013.
4. New Regulatory Rules for clinical Trials in United States and the European Union.
5. De Angelis C, Drazen JM, Frizelle FA et.al.Clinical trial registration: a statement from the international committee of Medical Journal Editors. Circ Res 2005;96:600-1.
6. International Ethical Guidelines for Biomedical Research Involving Human Subjects (3rd ed.). Geneva: CIOMS in collaboration with WHO. Retrieved 1 December 2014.
7. ICH Harmonized Guidelines for Good Clinical Practice E6 (R2) current step 2 version dated 11 June 2015.
8. Guideline for Industry. Clinical Safety Data Management: Definitions And Standards For Expedited Reporting.ICH E2A.
9. Reporting Of Serious Adverse Events In Clinical Trials To The Human Research Ethics Committee At Cahs: In accordance with the requirements as established by the NHMRC.
10. EU ICH E2F, European Medicines Agency 2010, Sep2010[EMA/CHMP/ICH/309348/2008 Committee for medicinal products for human use (CHMP)]
11. World journal of pharmacy and pharmaceutical sciences, Volume 5, Issue 8, 627-635 Review Article ISSN 2278 – 4357
12. Registration requirement for ethics committees. Central Drugs Standard Control Organization website. New Delhi,

India; Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Accessed on June 16, 2013.

13. U.S. Department of Health & Human services, National Institute of Allergy and Infectious Diseases(NIAID)
14. Therapeutic Goods Act 1989.
15. U.S. Department of Health and Human Services. Food and Drug Administration Office of the Commissioner (OC).Center for Drug Evaluation and Research (CDER)Center for Biologics Evaluation and Research (CBER).Center for Devices and Radiological Health (CDRH)Office of Good Clinical Practice (OGCP) January 2009.