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Comparison of Regulatory Submission Guidelines on Clinical Study Reports

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ABSTRACT

Background

A clinical study report is an "integrated" full report of an individual study of any drug conducted in patients, in which the clinical and statistical description, presentations, and analyses are integrated into a single report, incorporating tables and figures with appendices. ICH E3 Tripartite Guideline assist sponsors in the development of Clinical study reports. Beyond ICH regions there are variations in the data requirements in clinical study reports.

Objectives

To compare and find if any differences exist between selected non-ICH countries' guidelines on clinical study reports and ICH-E3 guideline.

Methodology

A systematic search was conducted using search terms in Google search engine and available guideline documents on structure and content of clinical study report (CSR) from the drug regulatory authorities' websites of Non-ICH countries were downloaded. India, China, South Africa and Singapore were selected as Non ICH countries and guidelines of these countries were compared with ICH E3 guideline.

Results

In the Indian guideline, the titles of sections are as for ICH-E3, but there are no sub sections to explain the data requirements. China guideline recommends different formats of clinical trials report for different phases of clinical studies (I, II & III) and Bioavailability/bioequivalence studies in addition to the sections of ICH E3. For South Africa, Clinical guideline recommends Summary Basis for Registration Application (SBRA). For Singapore, ICH E3 provides guidance on the organisation of clinical study reports, other clinical data and references within the ASEAN Common Technical Dossier (ACTD).

Conclusion

The study concludes that there are differences and similarities between the selected Non-ICH countries' guidelines on clinical study reports and ICH-E3 guideline. Non- ICH countries utilize ICH-E3 guideline as a reference document

Key words: Clinical study report, Guidelines, Non-ICH countries, Drug regulatory authorities

I. INTRODUCTION:

ICH stands for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH's logo has been designed with a view to representing the letters "I", "C", "H" in a manner which embodies the letters in an abstract human form.ICH- was established in 1990. Bringing together the regulatory authorities of the European Union, Japan and the United States and experts from the pharmaceutical industry in these three regions. ICH work Products- includes over 50 Guidelines on technical requirements (Quality - 20 Guidelines, Safety - 14 Guidelines, Efficacy - 21 Guidelines), Electronic Standards for the Transfer of Regulatory Information (ESTRI, E2B), Common Technical Document (CTD & eCTD), Medical dictionary for adverse event reporting and coding of clinical trial data (MedDRA) and Consideration documents[2].

By the late 1990s, ICH recognized the growing interest in ICH guidelines beyond the ICH regions. The Global Cooperation Group (GCG) was originally formed as a subcommittee of the ICH Steering Committee in 1999 in response to a growing interest in ICH Guidelines beyond the three ICH regions.

According to ICH -E3 guideline, the clinical study report is an "integrated" full report of an individual study of any therapeutic, prophylactic or diagnostic agent (referred to herein as drug or treatment) conducted in patients. Clinical Study Report is most critical document submitted as a part of the Common Technical document (CTD), masterpiece of a marketing authorization application, which represents the integrated full report of efficacy and safety data for an individual study of a therapeutic or diagnostic agent[6].

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II. METHODOLOGY

The method followed in this study includes the conduct of systematic search and then download available guideline documents on structure and content of clinical study report (CSR) from the drug regulatory authorities' websites of Non-ICH countries. Then Selection of four countries (India, China, South Africa & Singapore) from Non- ICH countries and then comparing the selected Non- ICH countries' guidelines on structure and content of CSR with ICH-E3 guideline and finding the differences between them if any. The data requirements which are given as main headings in table of contents of Structure and content of clinical study reports (ICH-E3 Guideline) are taken as a checklist for comparison of guidelines on Clinical study reports.

III. RESULTS & DISCUSSION

A systematic search was conducted using search terms in Google search engine. The Terms used for search includes Regulatory authorities, Drug regulatory authorities etc. Onsearch, found a document published by World Health Organisation (WHO). The document title was "List of Globally identified Websites of Medicines Regulatory Authorities". From this document, List of some of identified websites of Drug Regulatory Authorities of various countries of different regions (Africa, Eastern Mediterranean & Americas, South East Asia &Western Pacific and Europe) were represented in tabular form and available guideline documents on structure and content of clinical study report (CSR) from the drug regulatory authorities' websites of Non-ICH countries were downloaded. India, China, South Africa and Singapore were selected as Non ICH countries and guidelines of these countries were compared with ICH E3 guideline. The differences in data requirements between ICH E3 guideline and selected Non ICH countries' guidelines were presented in a tabular form.

Comparison of structure and content of clinical study reports:

	ICH (USA, EU & JAPAN)	INDIA	CHINA	SOUTH AFRICA	SINGAPORE
Title page	-Study title, name of test drug/ investigational product, indication -Name of the sponsor -Protocol identification (code or number) & development phase of study -Dates : initiation, completion , terminatio n -Name and affiliation of principal or	-Title of the study , the proto colco de, name of the investigationa l product , development Phase, indication -A brief descripti on of the trial design, - Dat es : initi atio n & com plet	-Tested drug generic name, the type of research and study number, -Dates : initiation, completio n of study principal investigat or (Signed), -Research institutes (seal), statistically Signature and -- -Seal Drug registration applicant (seal), -Contact information of the applicant for registration and date of	There was no Title page	Follows ACTD Part IV- Clinical document which recommends to follow ICH-E3

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	coordinating investigator(s) or sponsor's a responsible medical officer -Name of compan y/sponso r signator y -Statement indicating whether the study was performed in compliance with good clinical practices -Date of the report	ion The names of the Sponsor and the participat ing Institutes In Title page, There was no statement indicating study was performed in compliance with good clinical practices but it was given in another section and No date of the Report was given	reporting		
Synop sis	Usually limited to 3 pages numerical data to illustrate results, not just text or p-values.	1 to 2 pages (should summarize the important conclusions derived from the study)	Research Summary (with attached table)	There was no section like Synopsis or summary	

	ICH (USA, EU & JAPAN)	INDIA	CHINA	SOUTH AFRICA	SINGAPO RE
Table of contents	Page numbers for the locating various sections, graphs, tables, figures in the document	Only the Title -Table of contents without any explanation	Lists the contents of the directory of the entire clinical trial reports and the	No Ta ble of co	

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			corresponding pagenumbers	nte nts	Follows ACTD Part IV-Clinical document which recommends to follow ICH-E3
List of abbreviations and definition of terms	g i v e n	present but location different when compared ICH guideline	Abbreviations should be located in the first paper Glossary should given be at the end	No Abbreviations	
Ethics	-A list of all IECs or IRBs consulted should be given in appendix 16.1.3 -Declaration of Helsinki -Patient information and consent (Representative written information for the patient & sample consent form should be provided in appendix 16.1.3)	-Declaration of Helsinki A detailed description of the Ethics Committee constitution and -Date(s) of approvals of trial documents for each of the participating sites should be provided -A declaration as per Good Clinical Practice Guidelines issued by CDSCO & Ethical Guidelines for Biomedical Research on Human Subjects, issued by ICMR	- Declaration of Helsinki Ethics Committee (IEC or IRB) should review and approve the clinical trials.	clinical trials conducted in compliance with internationally accepted GCP guideline	

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	ICH (USA, EU & JAPAN)	INDIA	CHINA	SOUTH AFRICA	SINGAPORE
Investigators and study administrative structure	- Principal investigator, coordinating investigator, steering committee, administration, monitoring and evaluation committees, institutions, Statistician, central laboratory facilities, contract research organisation (C.R.O.), clinical trial supply management) The author(s) of the report, including the responsible biostatistician(s)	Study Team do not clearly specify who will be involved in the team like CRO	List of the principal investigators, research staff, Biostatistician	Information about the Investigators are not given	Follows ACTD Part IV- Clinical document which recommends to follow ICH-E3
Introduction	1 Page brief statement sponsor/company and regulatory authorities that are relevant to the particular study, should be identified or described.	A brief description of the product development rationale	drug research and development background, basis and reasonable, targeted indications Before treatment	There was no section with title introduction	

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			and the treatment effect; legal basis for the implementation of this study		

	ICH (USA, EU &JAPAN)	INDIA	CHINA	SOUTH AFRICA	SINGAPORE
Investigational plan	-Overall study design and plan – description (charts and diagrams), discussion of study design, including the choice of control groups -Selection of study population - (inclusion criteria & exclusion criteria ,removal of patients) - Treatments-blinding,prior and concomitant therapy ,treatment compli	-overall trial design, Subject selection criteria, -The treatment procedures, blinding / randomization techniques, - Concomitant treatment, efficacy and safety criteria assessed, -Data quality assurance procedures -The statistical methods planned for the analysis (	-Test design and the control group selection -Test process Efficacy and safety indicators -Data quality assurance -Statistical processing program and sample size determination -Test program modifications in Interim analysis	Includes patient population size and diagnosis, in- and ex-clusion criteria, test andcomparator / reference drug dosage regimens and duration of therapy, parameters assessed for efficacy andsafety	Follows ACTD Part IV-Clinical document which recommends to follow ICH-E3

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	ance -Efficacy and safety variables (primary efficacy variable(s) data quality assurance -Statistical methods planned in the protocol and determination of sample size -Determination of sample size change	Investigational plan was explained 3 lines whereas in ICH-E3 it was explained with sub sections in more than 6 pages)			

	ICH (USA, EU & JAPAN)	**INDIA**	**CHINA**	**SOUTH AFRICA**	**SINGAPORE**
Study patients	- Disposition of patients protocol deviations (Use of graphs, tables, figures for Clear accounting of patients who were enrolled, randomised & completed)	-Enumerate the patients screened,randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.	-A description of the subjects test program deviation (Recommends graphical representation of number of patients)	-The patient drop-outs should be addressed, including the time of and reason(s) for withdrawal/ drop-out.	Follows ACTD Part IV-Clinical document which recommends to follow ICH-E3
Efficacy evaluation	data sets analysed demographic and other baseline characteristics measurements of treatment	Limited information (Efficacy Evaluation	efficacy / effect analysis of data sets demographic and other	-Indications/Diagnosis. -Number of patients treated with each drug. -Dosage range	

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	compliance efficacy results and tabulations of individual patient data handling of dropouts or missing data multicentre studies drug dose, drug concentration, and relationships to response drug-drug and drug-disease interactions efficacy conclusions	was explained 3 lines whereas in ICH-E3 it was explained with sub sections in more than 5 pages)	baseline data compliance concomitant medications efficacy / effect analysis validity Summary	used. -Duration of treatment. Reference/comparative drug(s). - Parameters evaluated /findings. -Statistical data -Normally individual patient data from clinical trials need not be included in an application dossier	

	ICH (USA, EU & JAPAN)	**INDIA**	**CHINA**	**SOUTH AFRICA**	**SINGAPORE**
Safety evaluation	-Extent of exposure, adverse events (summary display analysis & listing) -Deaths, other serious adverse events, and other significant, adverse events Narratives, -Vital signs, Physical	-Complete list of all serious adverse events (expected or unexpected) and Unexpected adverse events whether serious or not, The comparison of adverse events, In tabular or graphical form.	Includes 3 levels 1. the subject medication / the extent of exposure (exposure), 2. common adverse events and laboratory means reasonable, 3. Serious adverse events and other important adverseeevents. Analysis of adverse events, security laboratory tests, vital signs and physical	Evidence of long term safety/efficacy Tabulate key long- term studies, their duration, indications, findings, tolerability, etc. with references, where applicable) (summary basis for registration application -SBRA)	Follows ACTD Part IV- Clinical document which recommends to follow ICH-E3

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	findings & other observations related tosafety - Clinical laboratory evaluation,analysis - Safetyconclusion - Dicussion and overall conclusion	brief narrative of all important events (Extent of exposure – duration, dose and drug cocentration, Vital signs , Physical findings & other observations related to safety, clinical laboratory evaluation were not given as sub sections, safety evaluation explains only about the SAE, AEs	examination, Analysis Tables, Summary of security, Discussion and conclusions (Similar to ICH guideline)		

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	ICH (USA,EU & JAPAN)	INDIA	CHINA	SOUTH AFRICA	SINGAPORE
Discussion and overall conclusions	-The efficacy and safety results, - Summary of risks and benefit, -The tables, figures, and sections, -New or unexpected findings, clinical relevance	Conclusions derived from the trial and scope for further development	-Summary of the efficacy and safety results of clinical studies, discuss and weigh the investigational drug interests -The possible problems should be read in conjunction with the literature reviewed to clarify the benefits	summary basis for registration application -SBRA	Follows ACTD Part IV-Clinical document which recommends to follow ICH-E3

The main findings of the study with respect to each country are given below.

INDIA

- India, Schedule Y Appendix II- and CDSCO draft Guidance -structure, contents and format for clinical study reports, the titles of sections are as for ICH-E3 guideline but does not give more information about the data requirements that are given as sub headings/sub sections with brief explanations and examples in ICH-E3guideline.
- India, Synopsis of the clinical study report is limited to 1 to 2 pages but in ICH-E3 it is limited to 3pages.
- For India, Statement of compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India is mentioned in separate section.
- The format of the References is not mentioned in the Clinical study reportstemplate.
- In Study objectives, primary and secondary objectives should bementioned.
- Annexures like Synopsis, Principal or Coordinating Investigator(s) Signature(s) or Sponsor's, Responsible Medical Officer, Study Design and Schedule of Assessments, Study Design and Schedule of Assessments, Disposition of Patients, Disposition of Patients, Listing of Patients Who Discontinued Therapy, Listing of Patients and Observations Excluded from Efficacy Analysis, Number of Patients Excluded from Efficacy Analysis, Guidance for Statistical/Analytical Issues which are clearly explained in ICH-E3 with examples are not given in the CSR template ofIndia.

CHINA

- China, guiding principles-The structure and content of the chemical drug clinical trials report is in Chinese language. Google translate is used to translate Chinese to English. There are few translationerrors.
- The references of this document are:

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1. FDA: Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (1988,July)
2. ICH-E3: "Structure and Content of Clinical Study Reports"(1995)
3. EMEA: "Day 70 Critical Assessment Report(2002)
4. SFDA: formal examination of points(2003)

- China guideline is similar to ICH-E3, as shown in the Table-5, but differs in the name of the heading/section for example Cover title instead of Title page, research summary instead of synopsisetc.
- China guideline recommends different formats of clinical trials report for different phases of clinical studies (I, II & III) and Bioavailability/bioequivalence studies in addition to the sections of ICH E3. This guideline provides samples of research reports cover title, the summary of the study, multi-centre clinical trial centres Summary andGlossary.
- In China, recommends a copy of the chromatogram and QC samples including the corresponding standard curve analysis in the list ofappendixes.

SOUTH AFRICA

- South Africa guideline 2.09 CLINICAL document is one among Guidelines- Human medicines ofMCC.
- On comparison with ICH E3, there are significant differences in Clinical document. The differences are shown in the table-5. There is no adequate description on contents of the document and only few sections/headings with sub headings aregiven.
- According to this document, normally individual patient data from clinical trials need not be included in an application dossier (except in the case of bioequivalence studies where the individual plasma/serum concentrations and derived pharmacokinetic data should be supplied).
- According to this guideline, randomised, double blind, placebo and/or active controlled trial design remains the gold standard for establishing the efficacy and safety ofmedicines.
- The Applicants should notify the MCC of: any approvals, rejections or withdrawals of applications in other countries, any serious adverse effects observed for the first time or at a frequency which has become a concern, new significant data which is contrary to the use of the medicine which becomesavailable.
- MCC recommends Summary Basis for Registration Application (SBRA). The SBRA is intended to be a very brief and concise document containing the core data, on the basis of which, the applicant intends to obtain registration for the product. It is to be presented as a summary only. Hence, e.g. no articles or reports should be incorporated into the SBRA, nor should such papers be attached to it either, as these belong with the fullsubmission.

SINGAPORE

- Singapore is a member of Association of Southeast Asian Nations (ASEAN). It follows ASEAN Common Technical Dossier (ACTD), for the registration of pharmaceuticals for human use. CLINICAL DOCUMENT is the Part IV ofACTD.
- ICH E3 provides guidance on the organisation of clinical study reports, other clinical data and references within theACTD.
- Clinical document consists of three sections namely- Table of contents, Clinical Overview and Clinical summary. Clinical overview should present the strength and limitations of development program and study results, analyse the benefits and risks of the medicinal product in its intended use and it should address the particular efficacy and safety issues encountered in development, and how they have been evaluated andresolved.
- Clinical overview includes overview of Biopharmaceutics, Clinical pharmacology, Efficacy, Safety and benefits and risksconclusions.
- Clinical Summary is intended to provide a detailed, factual summarization of all of clinical information in ASEAN common technical dossier. It is in the range of 50 to 400 pages (excluding attached tables). Clinical summary includes the summary of Biopharmaceutical studies, clinical pharmacological studies, clinical efficacy, clinical safety and individualstudies.
- In clinical summary of ACTD Part IV, ICH E3 is recommended to be followed in many of thesections.

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IV. CONCLUSION:

The study concludes that there are differences and similarities between the selected Non-ICH countries' guidelines on clinical study reports and the ICH-E3 guideline. Non-ICH countries utilise ICH-E3 guideline as a reference document. In the Indian guideline, the titles of sections are as for ICH-E3, but there are no sub sections to explain the data requirements. The China guideline recommends different formats of clinical trials report for different phases of clinical studies (I,II& III) and Bioavailability/bioequivalence studies in addition to the sections of ICH E3. Clinical guideline for South Africa recommends Summary Basis for Registration Application (SBRA), in which data should be presented in summary only. For Singapore, ICH E3 provides guidance on the organisation of clinical study reports, other clinical data and references within theACTD.

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