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Submission Requirements of Global Regulatory Agencies for Bioequivalence Reports: A Review

Hari Krishan Tiwari[1*], Arshad Hussain Khuroo[1]

[1]Clinical Pharmacology and Pharmacokinetics Department, Sun Pharmaceutical Industries, Research and Development, Sarhaul, Sector 18. Gurugram-122001, Haryana, India

**Address for correspondence-Hari Krishan Tiwari, Clinical Pharmacology and Pharmacokinetics Department, Sun Pharmaceutical Industries, Research and Development, Sarhaul, Sector 18. Gurugram-122001, Haryana, India*

ABSTRACT

The bioequivalence data is an integral part of the dossier application submitted to a regulatory agency for drug product approval. Each regulatory agency has a specific set of requirements for submissions. This review article provides a detailed description of specific bioequivalence reporting requirements and supporting documents for multiple countries. The bioequivalence data consists of the clinical phase, bioanalytical phase, pharmacokinetic, and statistical interpretations. This huge data is reported in the bioequivalence report and provided as a part of the dossier. The bioequivalence report shall be complete, free from ambiguity, well organized, and easy to review. This helps in the quick regulatory approval of dossier applications. This article aims to gather all the reporting requirements of bioequivalence studies at one place for various drug regulatory agencies globally. This will help drug manufacturers to get agency approval for marketing the drug products in a specific country.

Key words: Bioequivalence, electronic common technical document (eCTD), ICHE3, BTIF, ICH, ANDA.

I. INTRODUCTION

Medicines are a requirement of every human being on this earth. The cheaper, and affordable medicines are accepted by people across the world. Clinical trials on medicines are very costly. Therefore, a bioequivalence (BE) study is an alternative to clinical trials to reduce the overall cost of medicines [1]. Regulatory Agencies accept BE data in place of clinical trials for an abbreviated new drug application (ANDA) or 505(b2) applications as part of module 5 (m5) of the common technical document (CTD) and provide approval to market the medicines. In a bioequivalence study, the test drug product is compared with the reference product after oral administration to human beings. The biological matrix is collected at different time points and analyzed the matrix samples with chromatography techniques. The pharmacokinetic evaluation is done on the bioanalytical data. The statistical analysis is performed on the pharmacokinetic data to prove the test product is bioequivalent to the reference product.

The bioequivalence data is an important part of an ANDA or 505 (b2) application, which is filed to regulatory agencies to get generic drug approval. The BE data is submitted to the agency in m5 of CTD. The CTD submission to the agency electronically is known as an electronic common technical document (eCTD). The BE data is reported in the bioequivalence report as per specific regulatory agency requirements.

II. BIOEQUIVALENCE REPORT FORMATS

Generally, there are the following formats of bioequivalence reports recommended by regulatory agencies:

2.1 International Conference on Harmonization (ICH) E3
2.2 Resolution 895
2.3 ASEAN Bioequivalence Study Reporting Format
2.4 Final Report of an Interchangeability Study for Mexico Submission

2.1 International Conference on Harmonization (ICH) E3

This guideline is related to the structure and content of clinical study reports [2] and is recommended for adoption by the regulatory bodies of the European Union, Japan, and the USA. The objective of this guideline is to allow the compilation of a single core study report acceptable to all regulatory authorities of the ICH regions. This format is also acceptable for reporting bioequivalence studies and is well accepted by regulatory authorities of Canada, Australia, Gulf Countries, Malaysia, African Countries, WHO, and ICH regions. All the data related to clinical, bioanalytical, pharmacokinetic, and statistical phases shall be compiled as an integrated report along with relevant appendices to support the reported data. As per this guideline, the report should consist of sections 1.0 to 16.0. In sections 1.0, 3.0 to 13.0, the text is reported, which includes information about ethics, investigator's detail and administrative structure, introduction, objective, overall study

design and discussion, selection of study population, treatments, pharmacokinetic and safety variables, data quality assurance, statistical methods used in the study, changes in the conduct of the study (if any), study subjects, pharmacokinetic evaluation, safety evaluation, discussion, and overall conclusions. Section 2.0 is a synopsis which is a summary of all the phases of the study. In section 14.0, tables, figures, and graphs related to the evaluation of data are provided in this section. All the references are listed in section 15.0. Section 16.0 contains protocol, sample case report form, ethic committee details, sample consent form, curriculum vittae of investigators, signatures of investigators, listing of subjects receiving investigational medicinal products, randomization scheme, audit certificates, documentation of statistical methods, documentation of inter-laboratory standardization methods and quality assurance procedures if used, publications based on the study, important publications referenced in the report, discontinued patients, protocol deviations, patients excluded from the efficacy analysis, demographic data, compliance and/or drug concentration data (if available), individual efficacy response data, adverse event listings (each patient), listing of individual laboratory measurements by patient, when required by regulatory authorities, case report forms (CRF's), CRF's for deaths, other serious adverse events, and withdrawals for adverse events, other CRF's submitted, individual patient data listings, bioanalytical report and method validation report.

2.2 Resolution 895 (Rẻ 895)

This resolution of ANVISA (Regulatory Agency of Brazil) defines the reporting requirements of the bioequivalence report format. This report format is only acceptable for Brazilian submissions. Though Brazil's regulatory now accept ICH guidelines however they require BE reports as per their resolution. It is a modular format. This resolution can be referred to for detailed reporting requirements. It broadly contains general considerations, general information, protocol, ethics committee approval letter, and abbreviated curricula vitae of the principal investigator and those responsible for the clinical, analytical, and statistical stages. It also includes clinical report, standard operating procedures (SOP) of the clinical stage, protocol deviations, and their respective degrees of impact on clinical and pharmacokinetic results. This contains an analytical report, method validation report, analyte standards, and internal standards analysis certificates, standard operating procedures (SOPs) of the analytical stage: like analytical method, preparation, storage and acceptance criteria of stock solutions, calibration standards, quality control samples, dilution standards and reference solutions, to carry out the validation tests and acceptance criteria of the results, the performance and acceptance criteria of the analytical run, sample reanalysis and reporting of final concentrations, chromatographic analysis, sample reanalysis for anomalous values, reintegration of sample data, complete series of chromatograms of at least 20% of volunteers [3]. This report format also contains a statistical report, plasma concentration data, listing of the output (output) of the used statistical program [4]. The agency also requires a diskette or CD-ROM containing spreadsheets in MS Excel of the results of the pharmacokinetic parameters calculated individually and individual values of the plasma concentrations of the drug, separated by product.

2.3 ASEAN Bioequivalence Study Reporting Format

This format is acceptable by ASEAN countries [5]. The bioequivalence report (BE report) contains a title page with the name and address of the sponsor, name, person in charge and address of the Institution, name, and address of the principal investigator, name of medical/ clinical investigator, name, person in charge and address of clinical laboratory, name, person in charge and address of analytical laboratory, name, person in charge and address for data management, pharmacokinetics and statistical analysis, name and address of other Investigator(s) and study personnel, start and end date of clinical and analytical study, signature and date of investigator(s), (medical writer, QA manager – if applicable). It contains a study synopsis, table of contents, abbreviation and definition of terms, introduction, objective, test product, and comparator product information like name, batch numbers, expiry date, name and address of the manufacturer, etc. The BE report also contains pharmaceutical equivalence data, a comparison of dissolution profiles, letter with a signed statement from the applicant/sponsor confirming that the test product is the same as the one that is submitted for marketing authorization. It describes the investigational plan, clinical study design, study treatments, clinical and safety records, pharmacokinetic parameters and tests, statistical analyses, assay methodology and validation, data quality assurance, results and discussion, clinical study results, summary of analytical results, pharmacokinetic analyses, statistical analyses, conclusions. It also contains appendices like protocol, letter of approval from Regulatory agency (if applicable), study protocol and its amendments together with Institutional review board/ethical committee approvals, informed consent form, protocol deviation listing, adverse event listing, finished product specification, and certificate of analysis, validation report (including raw chromatograms), analytical report (including 20% of

raw chromatograms), certificate of the clinical facility, clinical laboratory and certificate of analytical laboratory, and dose proportionality comparative dissolution profiles between various strengths (when BE study investigating only one strength but application for registration consists of several strengths (from the sponsor).

2.4 Final Report of An Interchangeability Study for Mexico Submission

The Federal Commission for the Protection against Sanitary Risks is the regulatory agency for medicines control in Mexico. It is known as *Comisión Federal para la Protección contra Riesgos Sanitarios* (COFEPRIS). BE report is preferred to be submitted as defined in Mexican Norm Nom-177-SSA1-2013 [6]. It includes general information about the study title, the name of the clinical, analytical, and statistical units. The principal investigator should sign the report. It also includes the signatures of bio-analytical and statistical investigators. The final report shall also include the signatures of the quality assurance person and the study sponsor. The report shall consist of objective, scope, summary, and assed drug information like name, lot number, expiry date, manufacturer details, dose, etc. The clinical report shall be annexed with the final report. The clinical report shall contain detailed information on the clinical phase of the BE study. The analytical report shall be appended with the BE report. The analytical report shall contain a detailed description of the bioanalytical phase method details, validation details, calibration curve information, sample details, acceptance criteria of runs, bioanalytical results, and conclusions. The BE report shall be appended with the pharmacokinetic-statistic report. This shall include treatment description, descriptive statistics of the demographic variable data, individual data and average of the concentration in the biological fluid concerning sampling time and formulation, descriptive statistics of the concentration data, pharmacokinetic parameters data, ratio (test/reference), and the ratio logarithm for the pharmacokinetic parameters, ANOVA and the confidence intervals with statistical conclusion. BE report shall be appended with a copy of the list or announcement issued by the Ministry of Health where the reference drug is indicated as such, a letter under oath supported by the sponsor's sanitary responsible which confirms that the test lot submitted to the interchangeability test corresponds to the quali-quantitative formula. BE report shall include a copy of the letter issued by the sponsor where the test drug lot number is specified which complies with the nom-059-ssa1-2013, supported by the sanitary responsible, copy of the certificates of analysis that have the test drug lot and the quality control tests where the valuation and content uniformity is included and if applicable, dissolution; supported by the sponsor's sanitary responsible, protocol authorization copy and amendments when applicable, issued by COFEPRIS, copy of approval by the research ethics committee, sponsor's clinical monitoring report that includes: start of the study, monitoring reports and study closure, record of the adverse events report format, representative chromatograms of the validation method parameters, representative chromatograms of an analytical run from at least two research subjects from both periods (system suitability, calibration curves, control samples and research subject's samples), representative chromatograms of a reanalysis run (system suitability, calibration curves, control samples and research subject samples), method validation report to quantify biological samples, analytical report, pharmacokinetic-statistic report and biowaiver for other concentrations.

III. ELECTRONIC SUBMISSION

Electronic Common Technical Document (eCTD) submissions are accepted by various Regulatory agencies worldwide like FDA US, TPD Canada, EMA Europe, TGA Australia, WHO, NPRA Malaysia, SAHPRA South Africa, PMDA Japan, MFDS South Korea. Considering the FDA US electronic submission as a prototype, all the files of the BE report must be submitted in Portable Document Format (PDF) files [7]. The submission should not contain empty files and folders. Portable Document Format (PDF) files submitted must adhere to regulatory agency-defined specifications [8]. A report and its contents shall be submitted as PDF files of version 1.4 or above. Security settings or password protection for PDF files should not be included. A report and its contents shall be splitted into PDF file preferably as follows (i.e.): a synopsis, study report (section 1, 3 to 15), protocol and protocol amendments, sample case report form, ethics committee approval letter and sample consent forms, CVs/JDs of investigators and other important participants, signatures of study personnel involved in critical roles, listings of subjects receiving the test drug(s) / investigational products from specific batches, randomization scheme, QA audit statement / certificate, documentation of statistical methods, documentation of inter – laboratory standardization methods and quality assurance procedures-if used, publications based on the study, important publications referenced in report, COAs of the test and the reference product(s), discontinued subjects, protocol deviations, subjects excluded from pharmacokinetic analysis data, demographic data, compliance and /or drug concentration data, individual pharmacokinetics response data, adverse/ medical events listings (each subject), listing of individual laboratory measurements by subjects, case

report forms, bio-analytical report, method validation report.

The regulatory dossier should preferably contain the applicable PDF files. Documents will be provided as text-based documents preferably, rather than image files. The name of the files should reveal the contents inside it. The contents of the file should be with the file extension. The sixty-four characters are only acceptable to name the PDF file. While naming the files only letters in lowercase, numbers, underscores or hyphens in the name should be used. Blank space or special characters should be avoided in the file name. The length of the entire path of the file should not exceed 150 characters. For documents with a table of contents, provide bookmarks and hypertext links preferably for each item listed in the table of contents including tables, figures, references, and associated appendices. The bookmarks shall be created and matched within the document as per its table of contents. The navigation efficiency is also improved by providing hypertext links throughout the document body. The hyperlinks help to view annotations, references, related sections, appendices, tables, or figures within the same PDF as well as external PDF files within the same dossier. The hypertext links shall be created by rectangles using thin lines or by blue text as appropriate. The invisible hyperlinks should be created for a table of contents, and appendices. A list of tables and figures should also contain invisible hyperlinks. The magnification setting of inherit zoom should be chosen while creating bookmarks and hypertext links. The subject's unique identifier shall be used as the title of the document and the file name. The bookmarks shall be created within each case report form as per its table of contents. The electronic submissions gateway (ESG) [9] of the US FDA allows the secure dossier submission for regulatory review up to a size of 10 gigabytes or smaller preferably.

IV. BIOEQUIVALENCE DATA SUBMISSION IN DIFFERENT COUNTRIES

4.1 US submissions

US FDA submission shall go as an electronic Common Technical Document (eCTD) submission [7, 8]. The bioequivalence report (BE report) shall be organized and follows ICHE3 guideline [2]. BE report is submitted as a part of module 5 (m5) in eCTD. BE report is splitted into various PDF files as per eCTD granularity [7, 8]. Each PDF file should be prepared and meet the specifications of PDF guideline [8]. The following bioequivalence information shall also be available in eCTD: data summary tables of pivotal BE studies, Clinical Data Interchange Standards Consortium (CDISC), financial disclosures of investigators, FDA Form 3455 by the sponsor, GCP statement of investigators, Medical License of Investigators, data summary tables of pilot studies falling in similar category [10, 11].

Deficiency of information/record/data leads to the FDA to refuse to receive (RTR) [12] an ANDA application. An RTR decision indicates that the FDA has determined that an ANDA is not a substantially complete application (i.e., that the ANDA, on its face, is not sufficiently complete to permit a substantive review). One or more major deficiencies lead to RTR an ANDA. The minor deficiencies less than ten shall be quickly responded. The responses shall be submitted within seven calendar days to avoid RTR. Ten or more minor deficiencies lead to RTR an ANDA. Deficiencies related to bioequivalence data are mentioned here. Major deficiencies include (but not limited to): Only failed in-vivo BE study is submitted {90% confidence interval (CI) falls outside of the 0.8-1.25 acceptance criterion for AUC and/or C_{max}}, missing case report forms, and insufficient long-term stability in matrix. An ANDA contains one/more in-vivo study, that is not suggested under BE guidance without adequate justification, is also a major deficiency.

An applicant should provide long-term stability in biological matrix (LTS) coverage and data location in the bioequivalence report in summary table 10 [10]. As indicated in the table, the applicant should specify the exact location of the LTS reports and data in Module 5.3.1.4. The applicant should state the module, section, subsection, and pages. The applicant also includes a hyperlink in addition to the exact location.

The LTS data should be submitted in the dossier for the study. It should be available in module 5.3.1.4. It should also be provided in summary table 10. FDA will generally categorize an applicant's failure to provide LTS data either in summary table 10 or in module 5.3.1.4 as a minor deficiency. It is mandatory to include the LTS data in submission to avoid RTR [12].

The agency recommends that the BE data summary tables should be available in ANDA submission for the cross-referenced ANDA, at minimum. Depending on the type of study conducted, the applicant should provide appropriate summary tables for each applicable study within their submission. To facilitate the submission of this data, FDA has developed summary table templates to be utilized by applicants [10]. Generally, failure to provide the data in a summary table would be considered a minor deficiency. The applicant should provide summary data tables in module 2 for passed study. The whole study data should be available in m5. A failure to submit passing study data in respective modules would lead to an RTR determination.

A non-bioequivalent BE study should be avoided for submission. The agency can RTR the submission based on a failed in vivo study. It can be submitted along with a passed in vivo BE study. The in vivo BE study should be avoided in the submission that was not recommended in the guidance [12]. This can lead to RTR. An adequate explanation should include justification for an approach that deviates from FDA-posted guidance, including data (Module 2.7 and Module 5). An in vivo study does not contain copies of individual case report forms for volunteers who participated in the study, the FDA shall refuse to receive the application [12].

4.2 Brazil Submission

The bioequivalence report (BE report) shall be organized and follows Resolution 895 [3] and technical note 04/2014 [4]. This is specific to Brazil's regulatory submission. It is a modular format of the BE report. Apart from that a summary of the pilot or pivotal study conducted on the same batch, the model of declaration and identification of a BE study included in the application and a letter informing about other studies performed with the same test product shall be provided as a part of the application. The concentration data and pharmacokinetic data of subjects in MS Excel shall be provided on a diskette or CD-ROM [3].

4.3 Europe Submission

The submission is done electronically as eCTD. The bioequivalence report (BE report) shall be organized and follow ICH E3 guideline [2]. The report is submitted as a part of module 5. The report is divided into various PDF files as per eCTD granularity [13]. Each PDF file should be prepared and meet the specifications of PDF guideline [14]. The following bioequivalence information shall also be available in eCTD: module 2.7.1 tables of pivotal BE studies [15], a bioequivalence summary in module 2, pre-authorization GCP inspections-tables of study, and study report synopses (under ICH E3) for pilot studies, are required. The clinical study should meet the ethical requirements of Directive 2001/20/EC [14] if it is conducted outside European Union A statement of assurance from the sponsor shall be submitted in the dossier in module 1.9. A complete BE report for pilot studies should be available [15]. It can be requested by the agency. A summary data of pilot studies conducted during formulation development should also be included in Module 2.7 [17]. The study report synopses are sufficient.

4.4 Australia Submission

The bioequivalence report submission for the Therapeutic Drugs Administration (TGA), Australia shall go as mentioned for Europe. Additionally, the bioequivalence study information form (BSIF) and summary of the bioequivalence study are required to be a part of CTD [18].

4.5 New Zealand Submission

Medsafe is a regulatory body that ensures and controls the quality of medicines in the country [17]. International Conference on Harmonization (ICH) guidelines and EMA bioequivalence guideline are followed for Medsafe submission. The bioequivalence report (BE report) shall be organized and submitted in ICHE3 as per EU requirements [19].

4.6 WHO Submission

A bioequivalence report must be submitted in a product dossier [20]. It can be submitted in ICHE3 format. The report should precisely reflect all the phases of the study, its conduct and results. It should be well-written and presented. All the deviations should be reported in the report. The final report should include the bioanalytical report and method validation report of the study. These reports should describe the procedures of validated method and sample analysis. The investigators should authenticate the report. The report should also be signed by the sponsor. The bioanalytical report should be approved by the study director [20].

Furthermore, the dossier should also contain the bioequivalence trial information form (BTIF) in MS Word format for each bioequivalence study [21], a synopsis as per ICHE3 format for pilot studies (same formulation and manufacturing process), a summary of analytical runs in MS-Excel, concentration data of subjects in MS-Excel, pharmacokinetic data of subjects in MS-Excel [22]. The study synopses should be provided for all listed studies (pilot as well as pivotal) as a part of BTIF.

4.7 South Africa Submission

The South African Health Products Regulatory Authority regulates the safety and quality of medicines in the country [23]. The bioequivalence guidelines of the EMA are followed for this agency [23]. The bioequivalence report (BE report) shall be organized and follow ICHE3 guideline [2]. It is submitted as an electronic submission. Apart from that the bioequivalence trial information form (BTIF) in MS Word format [23], rregulatory inspection certificates, and monitoring statement. A bioequivalence summary shall be submitted as a part of the summary of critical regulatory elements (SCoRE) [24].

4.8 Sub-Saharan African Countries Submission

Sub-Saharan African Countries (SSA) follow WHO requirements. BE report shall be submitted to these countries as per ICHE3. A bioequivalence trial information form (BTIF) is also required to be submitted. BTIF as per WHO format

[23] can be submitted to most of SSA countries. Some SSA countries have their own BTIF formats, which need to be submitted like Tanzania, Uganda, Zambia, Zimbabwe [25], Nigeria, and Kenya.

4.9 Canada Submission

The bioequivalence report (BE report) shall be structured as ICH E3: Structure and Content of Clinical Study Reports [26]. It is submitted as an electronic submission in eCTD format [27]. Apart from that comprehensive summary of bioequivalence (CS-BE) [26], GCP/GLP statement along with regulatory certificates, .dat, and .inf files [26] are also required to be submitted.

4.10 Gulf Cooperation Council (GCC) Countries Submission

The report of the bioequivalence study shall give the complete documentation of its protocol, conduct, and evaluation. It shall be written per the ICH E3 guideline and be signed by the investigator. The name of the manufacturer sponsor of the BE Study with his approval and signature shall be included. The names and affiliations of the responsible investigator(s) shall be included in report. The detail of study sites, and the study periods shall be reported. Audit certificate(s) shall be included in the report. The report shall include the reference product formulation name with strength, batch number with manufacturer details, and expiry date. The country of purchase of the reference product should be included in the report. The details of the test product(s) used in the study shall be provided [17]. It includes a batch number, batch size, and name of the product. It should also include the manufacturing and expiry dates (if available) [17]. Certificates of analysis of reference and test batches used in the study shall be included in an appendix to the report. Concentrations and pharmacokinetic data and statistical analyses should be presented [28]. The GCC guideline is adopted from the EMEA guideline [17].

4.11 Philippines Submission

The Philippines Food and Drug Administration (PFDA) follows global guidelines such as ICH guidelines [29]. The study report shall be prepared as per ASEAN format or ICHE3. The BE report shall contain photos of the innovator sample with batch details, proof of procurement (storage condition, courier invoice), proof of purchase (pharmacy invoice), letter of approval from drug regulatory authority, informed consent forms (ICFs) for the trial subjects, COA of test and reference drug product, letter with a signed statement from the applicant/sponsor confirming that the test product is the same as the one that is submitted for marketing authorization must be provided. A valid certificate of accreditation and /or inspection report of the foreign BE site shall be provided to confirm compliance with GCP/GLP (clinical facility, clinical laboratory, and analytical laboratory).

4.12 Thailand Submission

ICH guidelines and other global standards, e.g. US FDA guidance, are recognized by the Thailand Food and Drug Administration (Thai FDA), Thailand [29]. The bioequivalence study reporting format defined in ASEAN guideline for the conduct of bioequivalence studies as well as ICHE3 are acceptable for submission. The ASEAN report format is described in this article.

4.13 South Korea Submission

ICH guidelines are generally accepted by the Ministry of Food and Drug Safety (MFDS), South Korea. The study report follows ICHE3. The submission in eCTD format is mandatory [29].

4.14 Taiwan Submission

The regulatory infrastructure is well developed in Taiwan. Taiwan Food and Drug Administration (TFDA), Taiwan follows most of the global standards. The study report shall follow ICHE3 [29].

4.15 China Submission

China Food and Drug Administration (CFDA) accepts the bioequivalence report in ICH E3 format [29] if CFDA-specific appendices are included: statistical report, approval letters from ethics committee, also for all protocol amendments, study site qualifications, principal investigators' qualifications, individual by-site summary for multi-center bioequivalence study (if applicable), certification of analysis and pre-production record (including placebo), package insert for comparator and investigational product (if marketed), chromatograms for samples from all subjects (bioequivalence studies). A bioequivalence study summary is required to be submitted in the dossier in CTD module 2. An eCTD is expected to be implemented at some point, the dossier is currently required as a paper submission. The study report and submission documents may be prepared in English, and then translated into simplified Chinese language for CFDA submission.

4.16 Japan Submission

Pharmaceuticals and Medical Devices Agency (PMDA) Japan follow ICH guidelines and BE report in ICHE3 shall be submitted to the agency. The details of the structure and content of ICHE3 are already mentioned in this article. The experimental conditions, subjects, drug administration, assay, and results of study shall be reported in BE report in ICHE3 format [30].

4.17 Malaysia Submission

Malaysia agency adopted ASEAN guideline. This guideline is further adopted from the EMA bioequivalence guideline [15]. The bioequivalence report (BE report) shall be organized and follows ICHE3 guideline [2]. The bioequivalence Study Report Submission Checklist shall also be submitted along with the BE report [31]. This checklist tells the ways of uploading the BE study report and other relevant documents in the Quest 3+ system [31]. Quest 3+ system is an online submission system for National Pharmaceutical Regulatory Agency (NPRA) to conduct secured online transactions for product registration, variation, licensing, market sampling, renewal, and other transactions.

The submission document shall be in searchable or optical character recognition (OCR) format and the text is legible. All documents in English or Bahasa language are required to be submitted for the agency review. The final BE report, including all the appendices, shall be submitted for evaluation. This is to note that the maximum single PDF file size in the QUEST 3+ system is 5MB. The BE report shall be splitted into multiple PDF files. A certificate of NPRA BE center compliance program issued by NPRA is required for the dossier submission. If it is not available then, a bioequivalence desktop evaluation (BEDE) acceptance letter issued by NPRA or proof of acceptance of the inspection application is required while applying to Malaysian agency [31].

4.18 Singapore Submission

Health Sciences Authority (HSA) Singapore accepts the bioequivalence study reporting format defined in ASEAN guideline for the conduct of bioequivalence studies as well as ICHE3 for submission.

4.19 Srilanka Submission

BE report shall include a complete description of the study conduct. It includes a description of experimental methods and materials, a presentation and assessment of the results, pharmacokinetic analysis, statistical analysis, and conclusion of study [32].

National Medicines Regulatory Authority Sri Lanka (NMRA) accepts the bioequivalence study reporting format defined in ASEAN guideline for the conduct of bioequivalence studies as well as ICHE3 for submission.

4.20 India Submission

The bioequivalence report should consist of an accurate, and complete description of the study. It shall include a description of the experimental, materials, and methods. The outcome of each phase of the study shall be evaluated, and statistical results shall be presented. Central Drugs Standard Control Organization (CDSCO) accepts the bioequivalence study report in any international format as per ASEAN guideline or ICHE3. It shall include protocol, conduct, results, evaluation, and conclusion [33].

V. CONCLUSION

ICH guidelines are widely adopted and there is increasing alignment with other global standards. However, each country generally has its local requirements. Furthermore, the regulatory environment is evolving worldwide, and it is important to keep up to date with current requirements to avoid delays in the submission and approval process. In addition to regulatory compliance, the quality of the data reporting with source data is important. The presentation of bioequivalence study data in one of the formats described in this article is essential for agency submission.

The focus of this article is to gather all regulatory agency reporting requirements at one place and submit the bioequivalence data without any deficiency by industry. All the bioequivalence report requirements and expectations of agencies are described in this review article. The most of the countries globally accept the bioequivalence reports in ICHE3 except Brazil and Mexico. The BE reports in country-adopted format with relevant appendices and supporting documents are required to assure the success of submissions and approval of applications.

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