An Overview of Clinical Overview

Raghu Rama Setty Alur, Freyr Solutions

Clinical Overview is a document presenting a critical analysis of Pharmacology, Efficacy, and Safety of the pharmaceutical agent. This document is developed for multiple objectives like product registration, justification for labeling document, and so on. A clinical overview helps the reviewer to understand the objective of the application and clinical development plan for a product in scope.

A Clinical Overview is an integrated document intended to provide critical analysis of Pharmacology, Efficacy and Safety of the pharmaceutical agent in humans. It is one of the important documents of Module 2 of the Common Technical Document (CTD) i.e., Module 2.5, which refers to the data provided in the comprehensive clinical summary, the individual clinical study reports presented in Module 5 and other relevant reports. It provides concise information about the conclusions and the implications of the clinical data provided in the dossier with a conclusive interpretation on the benefit-risk assessment of the medicinal product in scope.

The main sections of a Clinical Overview include product development rationale, overview of biopharmaceutics, overview of pharmacology, overview of efficacy, overview of safety, benefits and risks conclusions and applicable references. The CTD enables the customisation of the subsections based on the requirement, purpose of the clinical overview and the data available for the specific product in scope.

A Clinical Overview provides a brief discussion and interpretation of safety and efficacy findings related to the product, along with other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications), based on the findings from the clinical studies and/or published literature. Providing thestrengths and limitations of the development program and study results help in analysing the benefits and risks of the medicinal product for its intended use. It serves as a reference to the overall clinical assessment of the product and supports the information provided in the prescribing information.

The Clinical Overview is developed for a variety of requirements in today's scenario. Accordingly, there are two (2) types of Clinical Overviews: The Prospective and Retrospective Clinical Overviews. A Prospective Clinical Overview can be solely developed based on studies conducted by the innovator (for a new drug application to get the product registration) or data from studies conducted by the innovator and published literature data

(for a hybrid application or 505b2 type of submissions, wherein the applicant rely on some of the safety and efficacy information derived from the Clinical Studies conducted by the Original Innovator) or solely developed by using data from published literature references (for Generic submissions or other submissions such as “Well Established Use” or “Bibliographic Submissions”). In all the above situations, the purpose of the Clinical Overview is to support the application as a part of marketing authorisation.

With regards to Retrospective Clinical Overview, this document is generally not submitted to regulatory agencies as a part of registration dossiers. However, it is developed as a substantiation/justification for the core labelling documents (e.g., Company Core Data Sheet (CCDS) or Company Core Safety Information (CCSI)) developed by the innovator, to have company’s standpoint on the information related to safety and efficacy of a particular medicinal product in scope.

When a Marketing Authorisation Holder (MAH) has multiple registrations for a product across the globe, the format and extent of content (volume and depth of information) of the product information available in each country’s labelling document vary significantly. This creates an ambiguity to consider what is the actual safety and efficacy information of the product in scope. In these situations, the MAHcan select one of the registered country’s labelling documents as Reference Safety Information (RSI) or create Core labelling documents (CCDS or CCSI).

In experience, most MAHs prefer to develop the core labelling documents to represent the Company’s standpoint on the safety and efficacy of a particular medicinal product by using all the relevant information already available with them for that product, hence the term used retrospective development. The process would not end by developing only core labelling documents, it is required to develop the justification or substantiation document for the information available in the core labelling documents. This is the beginning of the development of a retrospective Clinical Overview to have the evidence for the safety and efficacy information available in core labelling documents. This process is evolving and every time there is an update to core labelling documents (life cycle management), the Clinical Overview also needs to be updated to provide evidence to the changes made to core labelling documents.

The update to Core labelling documents can be either safety or non-safety related. The trigger to update can be internal or external. Internally driven changes are based on safety monitoring, resulted from post-marketing studies or post-authorization safety studies, and may be due to open signals,whereas the externally driven changes include the changes suggested by Regulatory Agencies. Whether the safety changes are internally driven or externally driven, post-validation of the changes, the update to core labelling documents, country labelling documents (in case of Agency driven) along with the justification document (Clinical Overview) is required. As the Clinical Overviews developed for internally driven or externally driven safety changes related to specific safety information and only safety section of the Clinical Overview needs to be developed, these are termed as Abbreviated Clinical Overviews.

Additionally, these simpler versions of the Clinical Overviews are developed and submitted to Regulatory agencies as a part of life cycle management activities and/or market extension for a particular medicinal product. These overviews are used to substantiate the labelling changes during the post-approval part of the medicinal product's/drug's life cycle. Apart from internally or externally triggered safety changes, these overviews can focus on the specific update to the labelling documents related to efficacy, pharmacology or any other information. These overviews are termed as Abbreviated Clinical Overviews (ACO), Addendum to Clinical Overviews (ACO), Tailored Clinical Overviews (TCO), Customised Clinical Overviews (CCO), etc., as these documents are confined to specific information updates related to the medicinal product. Although the terminologies may differ based on the company's specific processes, the purpose it serves is the same.

Irrespective of the type of Clinical Overview and the time of its submission, the level of evidence is very important. When the Clinical Overview is developed solely based on the clinical studies conducted by the sponsor for a new chemical entity, it is the first consolidated document that talks about the product's safety and efficacy. In this scenario, the Clinical Overview should reveal the strengths and limitations of the clinical development program and study output. It should also provide the benefits and risks of the product for the intended use.

When the Clinical Overview is developed for Hybrid applications or the evidence comes from both the studies conducted by the sponsor and the literature data, the purpose and development strategy of the Clinical Overview should be clearly presented to help the reviewer. Development of hybrid Clinical Overview may trigger by introducing some novelty to the existing approved product. This may be a change in indication, new indication, new dosage form, new strength, new route of administration, new combination, new presentation, new target population (introducing paediatric indication), etc. The pros and cons of the change must be mentioned with the available evidence.

In a scenario where the Clinical Overview is developed entirely based on literature data (for generic or bibliographic or well-established use submissions), it is very important to consider the level or quality of evidence (hierarchy of evidence) to identify the literature articles. It is recommended to take help from medically qualified personnel in this process. In general, the well-accepted quality of evidence can be presented based on preference as follows.

- Clinical Practice Guidelines
- Meta-analysis and/or Systematic reviews
- Randomized Controlled Trials
  - Active Treatment Controlled Trials
  - Placebo Controlled Trials
- Uncontrolled Trials
- Cohort Studies
- Retrospective Studies
- Case Series
- Case Reports
- Expert Opinions

• Narrative Reviews
• Editorials

In the cases where a lot of information is available, the literature with highquality evidence would be preferred to use to develop the Clinical Overview. It is acceptable to omit the lower level of evidence when a significant amount of data is available with a high level of evidence. Few other points to consider while identifying the information for Clinical Overview are the impact factor of the journal, relevance of the information, the objective of the article, statistical parameters used, results of the trials or meta-analysis, statistical significance, power of the study, subset of the population enrolled, efficacy or safety parameters used and precision of analytical methods used (but not limited to).

The information mentioned in each subsection of the clinical overview should be relevant to the subsection with the proper flow of the information. This helps the reviewer to understand your case and the objective of the document. Below is the information that can be covered in each subsection of the Clinical Overview.

Product Development Rationale section should provide the details on pharmacological class of the product, give details on the pathological conditions in which the product is intended to be used, describe the existing therapeutic options available for the current condition in scope, how the product in scope is superior with regards to safety and/or efficacy or improve the condition/ compliance (once daily versus multiple administrations, oral administration versus parenteral administrations,) etc. This section should also cover the clinical development programme with details like completed, ongoing and planned clinical studies and the basis for the application. A summary of the scientific advice received (if any) from the regulatory agency can be provided.

Overview of Biopharmaceutics should represent the critical analysis of the problems related to bioavailability or bioequivalence of the product that might directly or indirectly affect the safety or efficacy of the product in scope. In case of generic submissions with Bioequivalence studies are part of the submission, a summary on the bioequivalence parameters and how the marketed formulation is equivalent to reference products (90% confidence intervals for Cmax, AUC 0-t and AUC0-inf) can be provided. If there is any study conducted to show the influence of food on the product’s rate and extent of absorption can be provided.

Overview of Pharmacology should cover the information related to Pharmacokinetics and Pharmacodynamics of the product.This section should address pharmacokinetics in healthy subjects, patients and special populations (paediatric, geriatric, pregnant women, lactating mothers, patients with renal impairment, patients with hepatic impairment, obese patients, cancer patients, patients with human immune deficiency virus, etc.). It also covers intrinsic factors (age, sex, race), extrinsic factors (diet differences, smoking, concomitant drugs) and pharmacokinetic interactions and their output. Details on rate and extent of absorption, distribution details, information related to metabolism and metabolites, excretion are included. With regards to pharmacodynamics, mechanism of action, receptor binding, onset of action, pharmacokinetics/pharmacodynamics relationships and pharmacodynamic interactions can be covered.

An overview of efficacy should provide the critical analysis of the efficacy of the product in intended use in the intended population. The analysis should cover the relevant data and should explain why and how the information supports the proposed use and the data in prescribing information. The quality of evidence should be considered and if there are any issues with efficacy parameters employed in the study or premature termination of the studies can be described with proper reasons. If there are any studies conducted in special populations, they should be clearly mentioned and if there are no studies conducted, support should be provided to extrapolate the efficacy data from the general population to the special population.

Overview of Safety should cover the critical analysis of the safety data with regards to adverse effects (details on common, nonserious and serious), warnings and precautions, drug interactions, safety in special populations, overdose and its management. The adverse events data should be provided in detail with relevant tabulations and frequency of the adverse events, nature of patient population and extent of exposure to be provided.

The benefits and risks conclusions section should provide the succinct, integrated and properly explained assessment of the product for the intended use. If multiple indications are proposed, the benefits and risks conclusions should be provided for each indication. This section should be developed based on the proper weighing of key benefits and the key risks without any ambiguity. Finally, a list of references used in developing the Clinical Overview to be listed.

--Issue 43--

Author Bio

Raghu Rama Setty Alur is a Pharmacologist with 16+ years of experience in Medical Writing, Clinical Research and Labeling. He has proven track record in developing the high-quality documents related to clinical, non-clinical and toxicological domains. He has few international publications to his credit. He has been part of Freyr for more than 5 years and currently heading the Medical Writing Department at Freyr. Raghu has successfully managed projects in the fields of clinical pharmacology, Medical Writing clinical and medical affairs, regulatory affairs, preclinical research, toxicology, and publication (Scientific) writing.