Non-Clinical Overviews to Support Marketing Authorization Applications in EU, Australia and Other Countries

Background

A top-10 North American generic pharmaceutical company with 300+ products saw its regulatory submissions requirements grow substantially due to increased product registrations in the EU, Australia and other countries. Since the Client teams did not have capacity and expertise to sustain their non clinical regulatory writing and submission work, they engaged Sciformix to author non clinical overviews (NCOs) as part of CTD dossier submission (CTD Module 2.4). The primary intent of NCOs is to provide an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the active ingredients. Due to the complexities and knowledge required for NCOs, Sciformix was able to fill this gap and successfully meet the client’s needs.

Regulatory Landscape

For any generic application in the EU region according to Article 10(1) of Directive 2001/83/EC as amended, and in derogation of Article 8(3) (i) “the applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials”. In terms of pharmaceutical/clinical equivalence, pursuant to Directive 2003/63/EC Annex Part II(2)(b), it is necessary to show that the finished product (generics) in application is essentially similar to the innovator finished product (reference medicinal product) as described in the Clinical Overview. On this basis, all information on the pharmaco-toxicological and clinical experience can be transferred from the originator product to the product of this application. For these applications, information about the pharmacological and toxicological characteristics of the product can be provided by submitting NCOs. Some health authorities such as TGA (Australia), MCC (South Africa), CIS (Russia, Ukraine, etc.) and LATAM countries (Brazil,
Solution

Sciformix quickly established a team of experienced regulatory writers with in-depth knowledge of pharmacology and toxicology, along with a medical reviewer to support the Client’s needs. The Client began sending NCOs to author after the team was familiarized with the Client’s processes. Sciformix developed a standard eCTD compliant template for NCOs that could be accepted across all regulatory regions. The template adheres to all the necessary requirements laid by the ICH and the EU directives including the overview of non-clinical testing strategy in-vitro and in-vivo, primary and secondary pharmacodynamics, safety pharmacology, PK and toxicity data in various animals species like rats, mice, dogs, rabbits and cynomolgus monkeys. The template also provides the reviewer important information about the safety of excipients and the impurities in the product. An integrated summary is also included to highlight the important safety topics and how the information included supports safe use of the product as per the proposed product label or SmPC.

Overcoming the Challenges

One of the key challenges in authoring NCOs for generic molecules is the literature search and selection of publications for inclusion in the integrated assessment. As generic molecules are generally well established molecules, a large amount of safety and efficacy data is available in the public domain. Therefore, literature search is a resource-intensive activity. With our experience and domain expertise, Sciformix’s expert writers have been performing systematic literature searches to address all specific points in the non-clinical assessment for multiple Client products. Over time, we have gained significant experience in designing the appropriate literature search strategy for Client’s using validated key words for molecules across all therapeutic areas. This comprehensive approach for literature search minimizes the efforts and is cost-effective for the Client. The primary activities performed by Sciformix include conducting detailed literature searches using Embase, Medline or Pubmed as well as specific toxicological databases like Registry of Toxic Effects of Chemical Substances (RTECS), the Hazardous Substances Data Bank (HSDB), Developmental and Reproductive Toxicology Database (DART), and Chemical Carcinogenesis Research Information System (CCRIS). Sciformix also takes into account recommendations provided by international societies for the regulations of products in a particular therapeutic area. For example, while authoring the NCO for antibacterial molecules, we considered the recommendations provided by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in addition to the EMEA regulations.
Draft NCOs undergo peer, editorial and medical review as part of our standard process to ensure quality and completeness. As required by the legislations, the NCOs are finally reviewed by an independent non-clinical expert who provides the declarations (CTD Module 1.4.2) to be submitted along with the CTD dossier. The non-clinical experts at Sciformix are globally recognized thought leaders and KOLs in the field of drug safety and risk management. Sciformix also helps the Client in responding to questions from health authorities i.e. request for additional details about specific non clinical testing issues, or biological characterization of impurities.

The team has been consistently providing high quality reports within the agreed timelines even during volume surges of up to 200%.

### Client’s Outcome

While this continues as an ongoing project, Sciformix has supported more than 100+ NCOs, including some complex ones (e.g. fixed dose combinations, branded formulations with limited published data, and products having potential genotoxic impurities or levels of impurities having out-of-specifications threshold etc.) for over 6 years. We continue to play a key role in helping our client achieve 100% compliance with regulatory submissions across their entire generic products portfolio.

Sciformix has been able to build a trusted partnership due to our flexible approach, willingness to adapt to the Client’s unique and growing needs, and ability to produce reliable, consistent and quality deliverables year after year. This partnership continues to evolve and we have become an integral part of the Client’s team.

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