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Editorial

Global Drug Development: Distinct Regulatory Requirements, Semi-harmonized Safety Requirements in Multiple ICH Regions

Ahmad Bayat[1]* and Shide Badri[2]

[1]*Director, Regulatory Affairs, Clinical Trial Project Manager, Amarex Clinical Research, LLC, Century Boulevard, Germantown, MD, USA*
[2]*Senior Vice President, Safety and Pharmacovigilance, Amarex Clinical Research, LLC, USA*

***Corresponding Author**: Ahmad Bayat, Director, Regulatory Affairs, Clinical Trial Project Manager, Amarex Clinical Research, LLC, Century Boulevard, Germantown, MD, USA.

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With the increasing globalization of drug (medicinal product) development, multiregional clinical trials (MRCTs) are becoming more and more popular in pharmaceutical industries. Many of pharmaceutical companies (referred to as Sponsors throughout this article) are relying on the data from MRCTs as the primary source of evidence to support marketing of their developing drugs. In November 2017, International Council for Harmonisation (ICH) published E17 guidance for planning and design of MRCTs and several regulatory authorities adopted their version after that. Although the E17 guidance opened a new door to the globalization of drug development, there are several regulatory and operational challenges in multiregional drug development. One of the main challenges is distinct and sometimes conflicting requirements from regulatory authorities.

The initial application for authorization of a clinical trial is called Investigational New Drug (IND) Application in the US and several Asian regulatory agencies while is referred to as Clinical Trial Application (CTA) in EU or Canada. Since May 2018, it became the United States Food and Drug Administration's (USFDA)'s requirement for all initial commercial INDs and the amendments to the commercial INDs to be submitted in electronic Common Technical Document (eCTD) format. Most of other regulatory authorities including European and Asian regulatory agencies require the Sponsors to submit their INDs/CTAs in either paper format or non-eCTD electronic format. As well as the need for the Sponsors of MRCTs to be compliant with different requirements of the regulatory authorities, they also need to be familiar with the different review processes and timetables for reviewing the CTAs/INDs in different regions. Each regulatory authority follows its own timetable for the review of initial CTA/IND which may cause disruption in the plan for initiation of a MRCT. Right after the submission, initial CTAs/IND applications are being validated for the completeness and compliance with the regional requirements first and then after the validation, the multidisciplinary scientific review will begin. Validation process varies from few hours (eCTD validation of initial INDs by USFDA) to few weeks (e.g. up to 25 days in the EU) prior to scientific review of the application. The scientific review process also varies between 30 calendar days (by USFDA) to few months. For most of the EU and Asian countries, it takes up to 90 days for the regulatory authorities to either authorize the trial or reject the application.

MRCTs which are planned to be used for support of marketing new drugs in ICH regions are expected to be conducted under Good Clinical Practice (GCP). GCP by definition is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. One of the requirements for GCP compliance includes approval of the clinical trial by an independent ethics committee (IEC) before initiating a study. Other includes but not limited to introducing a qualified investigator, description of clinical sites, and description of how the clinical study is being monitored to be conducted in consistent with the study protocol. The Sponsors can only initiate the trial after receipt of approval from both regulatory authorities and IEC.

Another important aspect of MRCTs is monitoring the safety of clinical trial. While the requirements for authorization of clinical trials and review of the efficacy of the data to support marketing differ in different ICH regions, the requirements for monitoring the safety of the investigational drugs and evaluating the safety of the drugs for approval are closer in different regions. The plan for global drug development should include a Safety Management Plan (SMP) which contains information about adverse event and serious adverse event recording and reporting. The SMP is required at any stage of a new drug development (i.e. during Phase I to Phase III Clinical Trials as well as Phase IV Clinical Studies and Post-marketing Safety Surveillance Studies agreed upon approval of a marketing application). A SMP usually includes Safety-related definitions and reporting requirements for expedited safety reporting. It should also include communication plans and various tools for proper and timely reporting of serious adverse events. This plan supports development and maintenance of Safety database which is the back bone of safety profile of new investigational product. Establishing an accurate and complete safety profile is critical for developing the product label at the time of marketing application submission and approval.

The following safety related regulatory timeline is widely adopted and implemented globally among different ICH regions: Sponsor (or designee) will provide written notification to the regulatory agencies and all participating investigators of any suspected adverse reaction that is both serious and unexpected. Each notification should be submitted as specified below, depending on the type of event. Each written notification may be submitted on specific form (i.e. USFDA form 3500A or CIOMS Form-I).

- 7-Day Expedited Report: Any serious and unexpected suspected adverse reaction that is fatal or life-threatening will be reported as soon as possible and in no later than 7 calendar days after the Sponsor's (or designee's) initial receipt of the information.
- 15-Day Expedited Report: Any serious and unexpected suspected adverse reaction that is not fatal or life-threatening will be reported as soon as possible and in no later than 15 calendar days after the Sponsor (or designee) determines that the event qualifies for reporting.

Although Chinese FDA (CFDA) adopted the ICH guideline, the requirements for reporting of adverse events to CFDA are slightly different in which all the severe adverse reports should be reports.

For periodic reporting of safety events of drugs under development, most of the Sponsors of MRCTs prefer to use a Development Safety Update Report (DSUR) as a common standard during conduct of MRCTs among the ICH regions.

This is usually expected that the country which the drug is planned to be marketed be among the countries that MRCT is being conducted, it is not mandatory that the country must be among them. For example, USFDA may accept the data from a well-designed and well-conducted clinical study outside of the US to support marketing application for a drug in the US if the study is conducted in accordance with GCP and if FDA deems it necessary, is able to validate the data through and inspection of the site [1-3].

In summary, while requirements of monitoring and assessing the safety of MRCTs seem harmonized in different regions, there is a need for harmonizing regulatory requirements by the authorities of different regions for more successful MRCTs.

Bibliography

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