ELECTRONIC MANAGEMENT AND TRANSMISSION OF SAFETY DATA: CURRENT STATUS AND NEXT STEPS

AUTHORS:
RAFAEL SMETS, MEDICAL AFFAIRS MANAGER, SGS LIFE SCIENCE SERVICES
ZUZANNA KWADE, PHD, MEDICAL AFFAIRS ASSOCIATE, SGS LIFE SCIENCE SERVICES
ANNICK VAN RIEL , DIRECTOR MEDICAL & REGULATORY AFFAIRS, SGS LIFE SCIENCE SERVICES

INTRODUCTION

In an industry where the global pharmacovigilance is a complex network of regulatory authorities, product approvals and licensing agreements, efforts need to be made to harmonize and computerize adverse event management and reporting across regions. The challenge of managing the safety risks of a pharmaceutical compound starts with accurate, timely and complete data about adverse events. Failure to effectively manage safety data can affect the well-being of patients, jeopardize the reputation of a company, and impact key relationships with regulatory authorities. Therefore, harmonization and improvement of the data quality is of major importance.

Over the last 10 years, Individual Case Safety Reports (ICSRs) have increasingly shifted from paper-based to electronic reports. Electronic transmission of individual safety information has become an essential component of global pharmacovigilance. In the European Community, the electronic reporting of adverse reactions became mandatory for both developmental and authorized products. Developed in 1997, the International Conference on Harmonization (ICH) guidance *E2B Data Elements for Transmission of Individual Case Safety Reports* established the concept of the standardization of the data elements for the transmission of ICSRs and led to the eventual release of *Electronic Transmission of Individual Case Safety Reports Message Specification,* prepared by the ICH Electronic Standards for the Transfer of Regulatory Information (ESTRI) Expert Working Group (M2).

Building on this experience, the E2B standard undergoes regular revisions to provide conventions for the harmonized interpretation of requirements and improve quality and consistency of electronic submissions.

CLINICAL SAFETY DATA MANAGEMENT: TRANSMISSION AND PROCESSING OF ICSRS

The successful electronic transmission of information relies on the definition of common data elements and standard transmission procedures. The objectives of the initial version of the ICH E2B guidance were to identify and define the data elements for the transmission of all types of ICSRs regardless of source and destination. This includes case safety reports from both pre and post approval periods and covers both adverse drug reaction and adverse event reports. Considering the high volume of data and the large number of potential participants in a world-wide exchange of information, there is an ongoing need to enhance electronic transmission of safety reports in a format that can be generated and processed automatically by a database application. This need has led to periodic revisions of the initial E2B guidance document.

In November 2000 and February 2001, the ICH issued the revised guidance E2B(R1) and E2B(R2), respectively, to provide additional information and clarification on data elements and message specification. The revised guidances incorporated adjustments based on the successful pilot

projects being conducted in the three ICH regions, the European Community, Japan and the United States.

In November 2009, the EudraVigilance Expert Working Group (EV-EWG) released a revised version of the N*ote for Guidance Eudravigilance Human - Processing of Safety Messages and Individual Case Safety Reports* applicable to all stakeholders who are exchanging ICSRs electronically in the European Economic Area (EEA) in line with the Community legislation[1]. The scope of this revised Note for Guidance is to improve the quality and consistency of ICSRs reported electronically to EudraVigilance. This has been achieved by strengthening the validation process of the ICH E2B(R2) data elements and by making the population of certain data elements in ICSRs mandatory. From 01 June 2010 onwards, the European Medicine Agency (EMEA) will perform a routine data quality control based on the updated business rules and validation process. Senders will receive monthly listings of ICSRs which do not comply with the new, mandatory data elements and validation rules as described in the revised Note for Guidance. A corrected version of the non-compliant ICSRs will have to be retransmitted by the sender to Eudravigilance immediately and no later than 15 days following the receipt of the listings.

FUTURE ICSR SPECIFICATIONS

Electronic reporting of ICSRs based on the ICH E2B(R2) standard has been implemented quite rapidly across the ICH regions. However, two major concerns have been raised during the implementation process. First, lack of mechanism in place that allows fast and efficient response to maintenance issues, and second, an increasing disharmony in the E2B(R2) data elements and their electronic transmission specifications (M2) between the regions. As such, the goal of a single transmission to multiple receivers in the three regions has not been achieved, jeopardizing the huge effort that has been made since 1997 to reach a consensus on this aspect. This resulted in pharmaceutical industry and regulators investing substantial human and financial resources in order to comply with different regional requirements. Achieving the goal of a fully harmonized implementation of E2B(R2) required the reopening of the E2B(R2) guideline to accommodate the resolution of all issues.

In May 2005, a revised guideline for *Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (E2B(R3))* was released for public consultation. In 2006, the decision was made that the ICH would pursue a new model for the development of the ICH M2 messaging standard to support the third revision of E2B. The ICH Steering Committee has taken a key decision that technical specifications should no longer be developed solely within ICH, but should be created in collaboration with Standards Development Organizations (SDOs) to enable wider inter-operability across the regulatory and healthcare communities.

The International Organization for Standards (ISO), Health Level 7 (HL7) and European Committee for Standardization (CEN) have formed the Joint Initiative through which a single, common standard for the ICSR could be advanced. The new standard, currently described in two draft ISO documents, will support a wide range of product types, including human medicinal products, veterinary products and medical devices.

The new final ICSR standard is to be published in January 2011. The ICH proposed to use the ISO standard to meet the reporting requirements for E2B(R3). However, the current M2/ E2B(R2) ICSR standard and the future ISO/E2B(R3) standard are structured in different ways. Therefore, it is obvious that there will be a time of transition until all stakeholders (regulators, pharmaceutical industry and other parties in the pharmaceutical business) have implemented the new guidelines and have their pharmacovigilance databases adapted to these new standards.

This implies that pharmacovigilance databases operating ICH E2B(R2) and/ or ICH E2B(R3) standards will temporarily coexist and that mapping procedures should be in place to ensure a coherent and harmonized exchange of ICSRs between all stakeholders at the international level. This is even more important since the exchange of ICSRs takes place between multiple senders and receivers and therefore depends on the implementation status (E2B(R2) or E2B(R3)) of each party in each transmission.

As a result, it is of major importance to address the compatibility between the two guidelines and the relevant message specifications and to provide the mapping standards that will ensure a smooth transition phase. Therefore, a set of the ICH conversion rules have been developed to help organizations during the transition period to implement systems with a special focus on the technical rules for switching between the current standard and the new standard. These rules will be provided in the ICH Implementation Guide along with two XML stylesheets that will perform the conversion manually.

Within the EEA, the EMEA started the preparation of an EU implementation plan for ICSRs. In general, further development of EudraVigilance and the achievement of high quality of ICSR data remain the priority of the EMEA's work programme.

CONCLUSION

The lack of internationally harmonized standards related to safety information and terminology is hindering the scientific evaluation and comparison of data. This impacts in particular the exchange and management of safety information in expedited adverse reaction reports at the international level, which is the key aspect of drug safety. Hence, the adoption of a standardized electronic message across regions, agencies and other parties has become one of the top objectives of the ICH community. Latest developments in relation to the ICH E2B and M2/ ESTRI activities will impact the current structure of the ICSR. Whilst it is envisaged that the ICH E2B(R3) will improve the current standards, a comprehensive planning of the future upgrades of pharmacovigilance databases from all stakeholders involved is required.

With innovative study designs, optimal facilities and strong regulatory intelligence, SGS can favorably impact client's drug development timelines and decision-making process.

REFERENCES

[1] Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, Directive 2001/20/EC, Volume 9A and Volume 10 of The Rules Governing Medicinal Products in the European Union.

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CONTACT INFORMATION

EUROPE
+ 33 1 53 78 18 79
clinicalresearch@sgs.com

NORTH AMERICA
+ 1 877 677 2667
clinicalresearch@sgs.com

WWW.SGS.COM/CRO