E2B (R3) - New challenge in pharmacovigilance - understanding evolution for safety reporting in EU

New challenge in pharmacovigilance?

Come on, you should be familiar with this situation, pharmacovigilance is nothing but more and more new challenges. What's new out there? Well, not so new, but it is the time to deal with that. It is the new E2B (R3)! Read the following as to get informed on the most significant challenges that your organizations should overcome, in order to comply with E2B (R3). This aims to introduce the content of the new EU Individual Case Safety Reports Implementation Guide (EU ICSR IG) which supplements the new ICSR ICH E2B (R3) and highlights the key changes between those and the current ICH E2B (R2) specifications. You will also find below approaches that your organization might consider for regulatory compliance in this aspect.

For more than a decade now, the exchange of safety information has shifted from paper-based to electronic formats. Electronic submission is a regulatory requirement in EU and across ICH (International Conference on Harmonization) regions, allowing safety information to be exchanged between multiple parties in a cost effective and harmonized way.

The electronic submission of adverse events is now performed in compliance with the ICH E2B (R2) specifications, current step 4 version, first approved in Feb 2001 by the Steering Committee. As soon as May 2005, ICH released a revised guideline, the E2B (R3), for public consultation. The creation of new rules for the reporting of ICSRs has become a necessity due to the evolving requirements of the Regulatory Authorities (RA). The International Organization for Standards (ISO) and several other organizations and committees collaborated as to respond to the necessity of a single standard for all product types and an unique identification of the medicinal products (IDMP standards), eventually leading to the ISO ICSR standard which was constrained by ICH to meet the data exchanged requirements for the ICH E2B (R3) specifications. ICH E2B (R3) is not using all data elements or requirements in ISO ICSR standard; other regions may nevertheless use the additional elements.

Following the release of the ICH E2B (R3) specifications in April 2013, the finalized EU ICSR IG was published on 21 Jan 2015 and is expected to be effective on 01 Jul 2016. The release of the ISO ICSR standard and of the associated ICH E2B (R3) specifications had given the organizations the opportunity to prepare for the implementation of the new ISO ICSR and for the replacement of the current E2B (R2) specifications. The EU ICSR IG addresses EU specific requirements in relation to the application of the ISO ICSR standard and the E2B (R3) package. The changes will affect both the pharmacovigilance and regulatory departments and will require key changes to

be implemented in order to comply with the requirements.

The following relationship exists between the ISO ICSR standard, the ICH E2B (R3) specifications and the EU ICSR IG:

The ISO ICSR standard (ISO/HL7 27953-2:2011) provides the schema files (technical structure) to be used to create ICSR messages.

• The ICH E2B (R3) specifications is a consensus document that provides the data elements for the contents of ICSRs as they will vary in usage across the ICH regions. Not all data elements and requirements from ISO ICSR were used.

• The EU ICSR IG supplements the ICH E2B (R3) specifications with additional EU specific requirements as to implement ISO ICSR standard in accordance with ICH E2B (R3) in EU.

Key differences between E2B (R2) and E2B (R3) supplemented by EU ICSR IG:

The structure of E2B (R3) is different than the current one in E2B (R2). In addition to that, the EU ICSR IG points out some additional requirements that should be used when submitting to EudraVigilance. E2B (R3) presents with new additional fields, fields that have been removed and/or modified and some data elements which have been moved from the case level to the event level. These changes will not only affect the look of the safety systems, but it will generally change the way that an adverse reaction will be captured.

➢ **Causality assessment in E2B (R3)**
  - Mandatory use of causality assessment for SUSARs (remains optional for the rest of expedited reporting). This method of assessment should be provided along with the EU Source of Assessment (e.g. investigator, sponsor, etc.) and the EU Result of the Assessment (Reasonable possibility or No reasonable possibility). The same assessment is used in E2B (R2) using the free text fields, whereas in E2B (R3) these fields are controlled vocabularies.
  - Implementation of ISO ICSR standard requires the use of controlled vocabularies for source, method and result of assessment (free text fields were formerly used in E2B (R2)).

➢ **Amendment reports**
  - In case of need of a correction (e.g. after internal review) or if a need arises to attach a document that was not available at time of the original report, an amendment report could be sent at a later time. Amendment reports need not alter

the case information (i.e. they are not follow-ups) and therefore the "date of receipt of the most recent information" field does not change between the amendment and the original report.

➢ **Attachments**
- E2B (R3) **allows attachments** such as literature articles or other documentation (e.g. autopsy reports, copies of lab results) to be incorporated in the ICSR xml file (previously it was not possible to attach documents to your reports). This new feature needs to be restricted for those documents that add value to the report (i.e. it is not intended for uploading full documentation of a case). The main use of this feature would be to attach literature articles (when requested).

➢ **Information moving from case to event level:**
- Seriousness
- Medical confirmation
- Country of occurrence

➢ **Characterization of drug role "Drug not Administered"**
- The code "Drug Not Administered", can be used for submitting events in clinical trials and for medication error cases.
- Trial events and medication errors can be reported as normal expedited cases.

➢ **Concept of null flavours**
- For specific reasons, information on mandatory data elements might be lacking for an ICSR that is still considered valid. Null flavour flags give a reason why this information is lacking (e.g. unknown, not provided).

➢ **Additional data fields and/or codes**
- Implementation of international standards for the Identification of Medicinal Products (IDMP) for human use in the EU (use of controlled vocabularies)
  o The ISO IDMP terminologies are not yet available for use with ICSRs. Current E2B (R2) terminologies or free text will be used by senders of ICSRs until they become available.
- New option for the field 'Patient age group'-'Foetus'.
- Coding **special situations** (in additional drug information field) - counterfeit, overdose, drug taken by father, misuse, medication error, expired lot, etc.
- Biological products
  o **Mandatory population of batch number field** for all suspect biological drugs (or else a null flavour)
- Device component
  o Additional fields: **Device ID, Device name, Device batch/lot number**

Both the E2B (R2) and E2B (R3) will be available for use during the transition period. A Backwards and Forwards Conversion (BFC) tool is also available to help the organizations, while preparing for the change.

The Impact of E2B (R3)

We are all well aware that the stakeholders will have to change their safety databases before E2B (R3) specifications become mandatory.

In order to be compliant to E2B (R3), the organizations will have to plan the process changes in advance and organize so that they are ready to perform both E2B (R2) and E2B (R3) submissions. However, it is not possible to have an E2B (R2) database and send E2B (R3) messages. E2B (R2) databases will only be able to receive the E2B (R3) safety messages and convert these to E2B (R2).

The changes described above will affect all SOPs and procedure documents as well as PSMF so they need to be revised. Significant re-training of all staff members involved in the process will be required. System testing should be planned well in advance to allow solution of any potential problems.

What ZEINCRO can offer?
➢ ZEINCRO can help you with **updating the SOPs** and work manuals based on E2B (R3) changes
➢ ZEINCRO can conduct the **training of the staff** in regards to the new changes and give possible approaches to deal with the problems with the implementation
➢ ZEINCRO offers complete range of **Pharmacovigilance and Device Vigilance Safety services**

References:

1. European Union individual case safety report (ICSR) implementation guide – *http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/04/WC500165979.pdf*

2. ICH guideline E2B (R3) Electronic transmission of individual case safety reports (ICSRs) - implementation guide - data elements and message specification – *http://www.ich.org/products/electronic-standards.html*

3. ICSR Public Consultation page – *http://estri.ich.org/index.html*

4. E2B(R3) Individual Case Safety Report (ICSR) Specification and Related Files – *http://estri.ich.org/e2br3/index.htm*

5. The new EU ICSR Implementation Guide - what you need to know – DIA ICSR Information Day – 29 Apr 2015 - Nick Halsey