E2B(R3):
THE INSIDE SCOOP FOR PRODUCT SAFETY TEAMS IN LIFE SCIENCES

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PREPARING FOR E2B(R3)

The electronic transmission of adverse event information to stakeholders, using the International Conference on Harmonisation "E2B" standard, is an essential component of global drug safety and pharmacovigilance operations. E2B(R3), the latest version of the International Standards Organization (ISO) Individual Case Safety Report (ICSR) standard, includes new requirements with which product manufacturers and the organizations that assist them with reporting safety information will be required to comply.

As with any new regulation, many questions have been raised around E2B(R3) that need to be addressed before life sciences companies can confidently implement the technology and processes they need to perform the day-to-day and periodic activities that support the regulations.

In an interview with Eugene Sefanov, marketing manager with Perficient's life sciences practice, Indy Ahluwalia, senior business consultant with the company's safety and pharmacovigilance team, provided insight into E2B(R3), the impact it is likely to have on drug safety business processes, and some ideas for how to move forward.

WHAT IS E2B(R3)?

E2B(R3) doesn't have a direct translation. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) published guidelines that have designated "E" to stand for efficacy. The work carried out by ICH under the efficacy heading relates to the design, conduct, safety, and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes, and the use of pharmacogenetics and genomics techniques to produce better targeted medicines. All "E2" guidelines relate to pharmacovigilance. The official E2B(R3) document is titled "Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports."

There was a time when people shared safety information on a hand-written forms. Then, E2B was introduced. E2B essentially defines what data elements need to be transmitted in individual case safety reports (ICSRs), regardless of the source or destination. E2B(R3) is actually the fourth major revision of E2B guidelines.

The FDA, EMA, and Japan's Ministry of Health, Labour and Welfare (MHLW) have all confirmed they will adopt E2B(R3) as their standard submission format. All companies that currently report safety data to regulatory agencies or partners using E2B will be required to adopt the new E2B(R3) format.

WHAT IS THE DIFFERENCE BETWEEN E2B(R2) AND E2B(R3)?

After the release of E2B(R2), the ICH realized that technical specifications should no longer be developed in isolation. E2B(R3) is the first technical specification to be developed through a new collaborative approach. The International Organization for Standards (ISO), Health Level Seven International (HL7), and European Committee for Standardization (CEN) collaborated to form the Joint Initiative on SDO Global Health Informatics Standardization, through which a single, common standard for the ICSR could be advanced. Subsequently, the Clinical Data Interchange Consortium (CDISC), the International Health Terminology Standards Development Organisation (IHTSDO), and GS1 became members of the Joint Initiative. ICH representatives have also been heavily involved.

The overall standard is based upon a HL7 ICSR model that is capable of supporting the exchange of messages for a wide range of product types (e.g., human medicinal products, veterinary products, medical devices).

E2B(R3) IS BASED ON THE INTERNATIONAL STANDARD HL7, WHICH ALLOWS A VARIETY OF CLINICAL SYSTEMS TO EXCHANGE DATA

The real benefit of E2B(R3) is interoperability, which ultimately better protects patients and consumers. Since E2B(R3) is based on HL7, a variety of clinical systems will be able to use it to exchange data with each other. With this new structure, more data can be passed to regulatory authorities or marketing authorization holders, making the information much more valuable to all parties involved.

HOW DOES E2B(R3) AFFECT COMPANIES WHO OPERATE IN DIFFERENT GLOBAL MARKETS?

Currently, two of the FDA branches have released guidance documents and have implemented a form of E2B(R3). Center for Biologics Evaluation and Research (CBER) has released "Providing Submissions in Electronic Format — Postmarketing Safety Reports for Vaccines" and the Center for Devices and Radiological Health (CDRH) has released "Technical Information on eMDR." While both of these branches have required E2B submissions since 2015, no new guidance has been published by Center for Drug Evaluation and Research (CDER), although the group is very likely to issue guidance sometime in 2016. Pending new guidance, if an organization manufactures vaccines or devices, it will likely be required to submit its safety data to regulatory authorities in the new E2B(R3) format.

Exactly when the European Medicines Agency (EMA) will require submissions to be in E2B(R3) format depends on the completion of a successful independent audit of the new EudraVigilance system, in addition to the implementation of the Identification of Medicinal Products (IDMP) guidelines. The audit will check that the required functionalities, agreed to by the Pharmacovigilance Risk Assessment Committee (PRAC) and the EMA Management Board in December 2013, have been implemented. The audit report, along with a PRAC recommendation, will be presented to the EMA Management Board, who will then announce whether the EudraVigilance system has sufficiently implemented the functionalities. This falls in accordance with EudraVigilance stakeholder change management plan. At the EMA stakeholder's day in December of 2015, the EMA stated that they hoped the requirements for mandatory submissions using E2B(R3) would be in place by in mid-2019.

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) has stated the interim period for submitting data in both E2B(R2) and E2B(R3) formats is between April 1, 2016 and March 31, 2019. Essentially, this suggests mandatary submission using E2B(R3) would begin April 1, 2019.

WHEN DO COMPANIES HAVE TO BEGIN COMPLYING WITH E2B(R3)?

In the United States, if a company is transmitting vaccine or device information to the FDA, it should already be reporting in E2B(R3) format. For companies reporting solely to the FDA Adverse Event Reporting System (FAERS), no official deadlines have been published.

UNITED STATES: COMPANIES TRANSMITTING VACCINE OR DEVICE INFORMATION TO THE FDA SHOULD ALREADY BE REPORTING IN E2B(R3) FORMAT

In Europe, drug companies who report to the EMA will need to comply with the new format by mid-2017, following the audit of the new EudraVigilance system.

EUROPE: DRUG COMPANIES WHO REPORT TO THE EMA WILL NEED TO COMPLY WITH THE NEW FORMAT BY MID-2017

In Japan, if a company transmits ICSRs to Japanese regulatory authorities, mandatory reporting using E2B(R3) is set for April 1, 2019.

JAPAN: COMPANIES WHO TRANSMIT ICSRs TO JAPANESE REGULATORY AUTHORITIES MUST USE E2B(R3) FORMAT BY APRIL 1, 2019

It is essential to note that if a company transmits data in the E2B(R3) format to a company whose systems do not accept it, the receiving company would need to convert the message into an E2B(R2) format, in order to make sense of it.

FOR A COMPANY THAT IS E2B(R2)-COMPLIANT, WHAT IS THE PATHWAY TO E2B(R3) COMPLIANCE?

Companies who are currently submitting reports using the format should already be planning the move to E2B(R3). If a robust safety and pharmacovigilance system is already in place, there are likely just a handful of technical changes that need to be made in order to meet the new regulations. For example, system configuration changes that affect reporting destinations could be required. That said, most companies will likely want to

IF A SAFETY SYSTEM IS ALREADY IN PLACE, THERE ARE LIKELY JUST A HANDFUL OF TECHNICAL CHANGES THAT NEED TO BE MADE

look at additional information that could be sent using E2B(R3) to provide a more robust ICSR.

HOW DOES E2B(R3) IMPACT ORGANIZATIONS THAT DO NOT REPORT VIA A SAFETY AND PHARMACOVIGILANCE SYSTEM?

The issue is not the type of system used to collect adverse event data, but rather how the data is submitted to the FDA, EMA, and MHLW. If an organization is using spreadsheets to collect safety data or is unable to transmit data via E2B, it will have to report the data via a web-based tool, such as the FDA's WebTrader or EMA's EVWEB.

DO 21 CFR PART 11-COMPLIANT, COMMERCIALLY AVAILABLE SAFETY SYSTEMS COMPLY WITH E2B(R3)?

Yes, some validated systems can comply with E2B(R3). With respect to Oracle Argus Safety, the current version, 8.0.1, is able to comply with E2B(R3), Electronic Vaccine Adverse Event Reporting System (eVAERS), and Electronic Medical Device Reporting (eMDR) reporting requirements.

ORACLE ARGUS SAFETY 8.0.1 AND ABOVE COMPLIES WITH E2B(R3) FORMAT

If a company is simply looking to meet E2B(R3) requirements, we advise waiting to upgrade until the EMA finishes testing and provides feedback to the industry. The testing should be completed by mid-2016. Nonetheless, organizations will not be able to transmit messages using the E2B(R3) format until after the audit of the new EudraVigilance, which is mid-2017.

If an organization has questions about whether a system is E2B(R3)-compliant, the software vendor or a reputable partner should easily be able to determine whether it meets regulatory requirements.

WHAT ARE THE IMPLICATIONS OF NOT COMPLYING WITH E2B(R3) BY THE DEADLINE?

In the European Union, the use of E2B(R3), along with IDMP, is in legislation, so not complying by the deadline could have legal repercussions. Non-compliance with the FDA and MHLW's requirements could also bring unwanted scrutiny. More importantly, if an organization does not comply by the deadlines, they will not be able to send ICSRs automatically to regulatory agencies. Nonetheless, if an organization's safety and pharmacovigilance system does not have the ability to submit data in the new E2B(R3) format, they can still transmit the information via web-based solutions, such as EMA's WebTrader.

ORGANIZATIONS WHO DO NOT COMPLY BY THE DEADLINES WILL NOT BE ABLE TO SEND ICSRs AUTOMATICALLY TO GLOBAL REGULATORY AGENCIES

Navigating regulatory guidelines and requirements is a challenge that all life sciences organizations must confront in order to protect the safety of patients, as well as to shield themselves from the dire consequences that can be imposed by global regulatory bodies.

As a company that has assisted hundreds of organizations with their clinical and safety system implementations and integrations, Perficient is in a unique position to help biopharmaceutical, medical device, and contract research organizations assess their situation and provide trustworthy recommendations they can depend on. While the commercially off-the-shelf adverse event reporting system we specialize in is Oracle Argus Safety, our team has the industry experience that organizations can turn to for all of their technology needs.

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Indy has been working in drug safety his entire career. After working on the operations side of the business, he moved to the technical side, specializing in pharmacovigilance systems and the industry's regulatory reporting rules. Most recently, Indy has been investigating E2B(R3), HL7, and IDMP to understand how they affect pharmacovigilance. He is also interested in the use of various technologies, such as social media, to help with signal detection. Prior to joining Perficient, Indy worked for Eisai, Amgen, and Gilead.

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