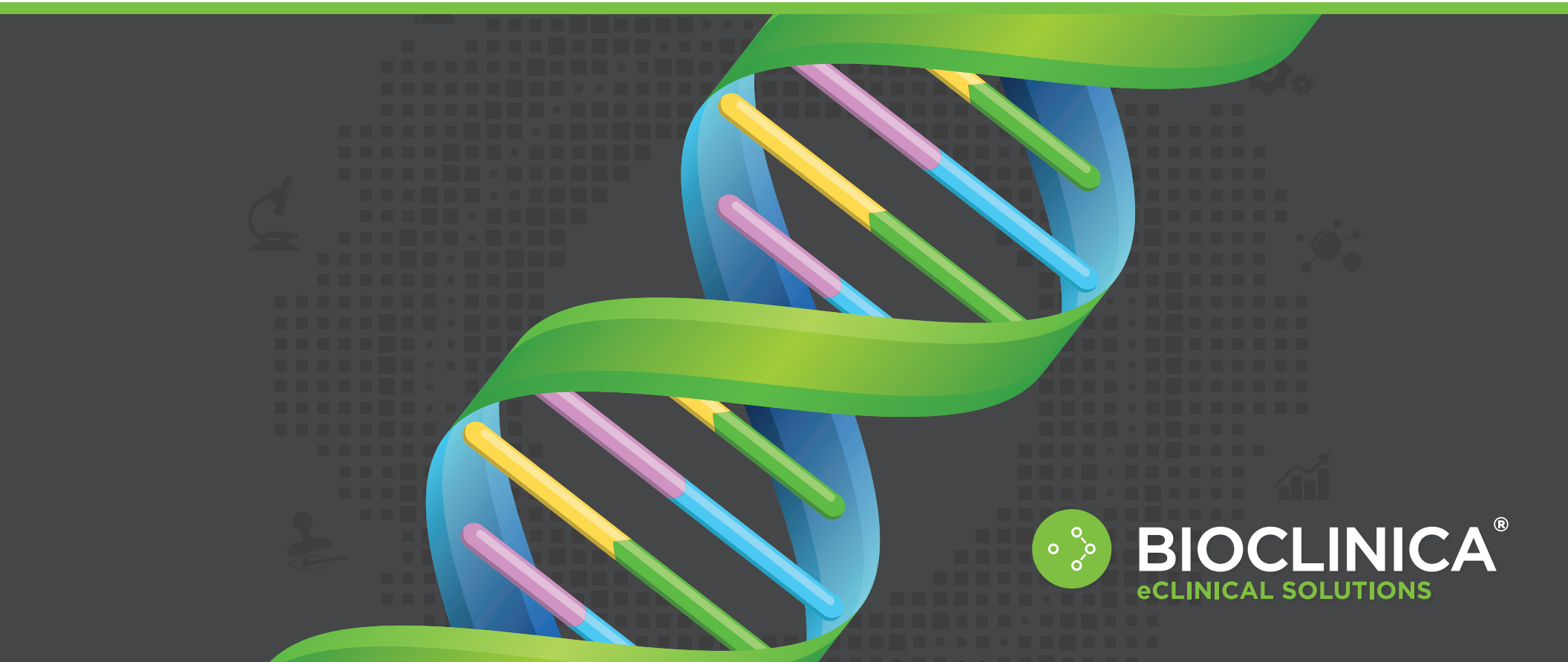
Finding the Right END-TO-END SAFETY SOLUTION for Your Needs

A Bioclinica White Paper



With upcoming changes, including the implementation of the International Conference on Harmonisation (ICH) E2B(R3) Electronic Transmission of Individual Case Safety Report and Identification of Medicinal Products (IDMP) standards, the current state of safety reporting can be confusing. Your existing safety system may not be flexible enough to accommodate these changing regulations, which are still moving targets regarding the details needed for a comprehensive solution with the right level of processes, company-to-company integrations and finalized regional rules.

Your end-to-end safety solution needs to encompass the required services, product and technology components to stand up to the challenges. Here, we provide an overview of the current state of safety reporting and why it has been confusing, discuss available solutions and the challenges they still pose and describe the qualities of an ideal safety partner that blends the services, technology and people that are appropriate for your capabilities and needs.

Current Safety Ecosystem

Regulatory authorities have long required that certain adverse events (AEs) are reported in a standardized fashion. The standards for submission of individual case safety reports (ICSRs) are currently being revised to improve the inherent data quality and to improve the handling and analysis of ICSRs.[1] However, a number of factors create a challenging environment in which to execute these new standards.

Identification of Medicinal Products

The IDMP standards aim to enhance the interoperability of systems internationally between global regulators, manufacturers, suppliers and distributors. These standards were initiated because of the early identification of a critical issue regarding the lack of harmonization in medicinal product information and terminology. The first key component of IDMP is a clear mapping of international terminologies for accurate comparisons and analyses of the routes of administration, dosage forms and units of administration. The second key component is the cross-border identification of medicinal products because there is a need to identify pharmaceutical products in situations where naming conventions and licensing identification vary as well as to identify a product's component substances even though they are not necessarily contained within a given safety report. To achieve these, a set of common global standards for unique identification of and exchange of information on medicines was developed, including data elements, formats and terminologies.[2]

There are currently five ISO IDMP standards in addition to the existing ISO standard (ISO 21090) (Figure 1):

- ISO 11238: Substances
- ISO 11239: Pharmaceutical dose forms, units of presentation, routes of administration and packaging
- ISO 11240: Units of measurement
- ISO 11616: Regulated pharmaceutical product information
- ISO 11615: Regulated medicinal product information

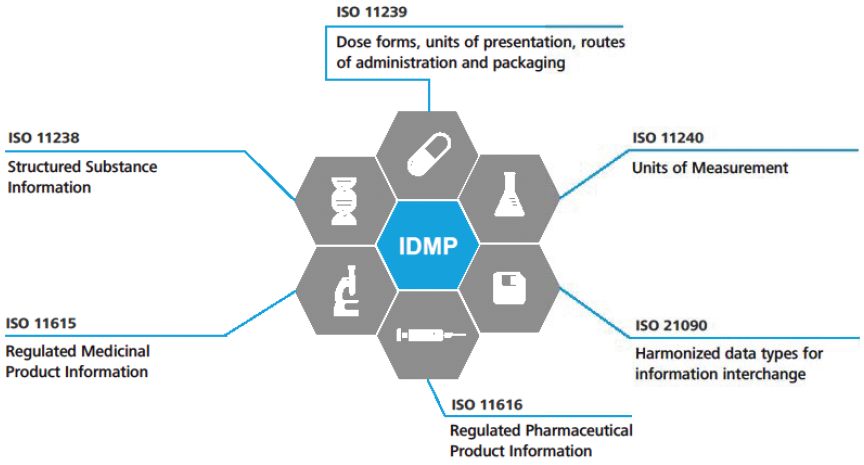


Figure 1. ISO standards for IDMP; Image source: Identification of Medicinal Products (IDMP): what is necessary to be compliant in 2016 and beyond? Available at: http://www2.deloitte.com/content/dam/Deloitte/ch/Documents/life-sciences-health-care/ch-en-life-sciences-the-challenge-of-idmp.pdf[3]

IDMP is still a work in progress, and the original plan stated that implementation of the IDMP standards would be mandated by now. The most recent estimate is two years from now. If the challenge were purely technical, we could adjust; however, there are also challenges for governance, including the need to work with multiple domains such as regulatory, quality and manufacturing; organization, with these groups not used to working together; and collaboration. Compliance with these standards requires a cross-functional effort to align standards, master the data management, perform data governance and identify authoritative source systems. The standards will also require data to be consolidated across the entire product lifecycle, including regulatory affairs, product supply, pharmacovigilance and clinical development. Given the breadth of the impact, there is limited time to consider the implementation and the changes needed for processes, systems and data governance.

E2B(R3) Electronic Transmission of Individual Case Safety Reports

With the introduction of E2B(R3), electronic submission of safety data is required, and a technical message for ICSRs has been developed in anticipation of the IDMP standards. Specific elements have been incorporated into this technical message to carry IDMP terminologies and Medicinal Product (MPID) or Pharmaceutical Product (PhPID) identifiers.

The following four items have been released as part of E2B(R3)[1]: ICH Implementation Guide, schema file set, reference instance XML files and backwards and forwards compatibility documents.

The ICH Implementation Guide supports the implementation of software tools for creating, editing, sending and receiving electronic ICSR messages. It also provides instruction for how the pharmaceutical industry and regulatory authorities will use Part 2 of the ISO standard to construct messages for exchanging pharmacovigilance information between and among themselves in ICH regions and in other countries adopting ICH guidelines. Finally, it describes the elements that might vary across the ICH regions; clarification and explanation of these variations will be defined by regional implementation guides.

The schema file set is a set of XML schema files containing the "constrained" set of rules, elements and attributes stemming from the HL7 v3 messaging standards that are used in Part 2 of the ISO ICSR standard and are required to construct ICH-acceptable ICSR messages. It provides the technical files required by the IT tools that actually construct, export, read or validate the messages.

The reference instance XML files consist of an example file that illustrates the coding of an ICSR according to the constraints encoded in the schema files and in compliance with the ICH Implementation Guide. This is an illustrative example that does not contain real information. A second example file provides a similar illustration of an Acknowledgement message.

The backwards and forwards compatibility documents describe the relationship between elements from E2B(R2) and E2B(R3) and assist reporters and recipients (including pharmaceutical companies, authorities and non-commercial sponsors) in implementing systems with a special

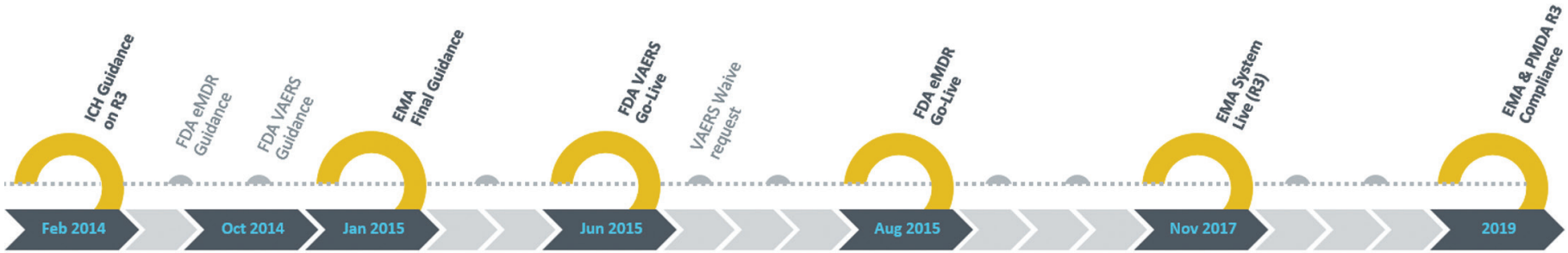


Figure 2. E2B(R3) timeline as of August 2016

focus on the rules for conversion back and forth between the previous standard. They also include mappings of the elements against one another, with an explanation of the differences and guidance on how to convert between the message structures and address issues with compatibility.

So, what needs to happen now? The implementation guide addresses a harmonized approach to ensure backwards and forwards compatibility between the current ICH ICSR message specifications and the new standard—a major aspect during the transition phase until all stakeholders have upgraded their pharmacovigilance systems to handle the new standard.[1]

It remains unknown what will remain after it is finalized.

Unaddressed Needs with the New Standards

Despite the improved standardization with the new standards, a number of unmet needs remains. The maintenance of multiple local regulations will require specific implementations and configurable local reporting. You might have to continue to use a paper form for a local agency, and the local entity will have to track the report. E2B(R3) does allow the inclusion of regionally controlled terminology[4] as well as region-specific elements, although they will be considered non-harmonized (e.g., race, ethnic group). In addition, configurable aggregate reporting might be required. For example, certain therapeutic areas or safety officers require specific reporting, and you will not want to recreate the reports every time.

It may be helpful to identify use cases for which you can improve productivity. You might want to determine how to embed corrective and preventive actions (CAPA) in the processing or reporting so that the system can be improved if you observe repeated mistakes or changes. Recognizing areas for improvement will also assist with Safety Data Exchange Agreement (SDEA) management, because the current system might not be meeting the obligations.

Embracing affiliates could enable you to expedite reporting, bring in legacy cases, become more creative and meet a more diverse set of needs. Moreover, you could more easily adopt new-age technologies with a pharmacovigilance core technology landscape, including big data, AI and open-source frameworks.

How Do You Choose Your Safety Partner?

To help you meet the new standard requirements, there is a number of potential safety partners, each with their own strengths and unique capabilities. Certain considerations must be made to make sure that your chosen partner meets your specific needs.

The typical solution from safety partners is that one size fits all, based on the belief that the standard should be followed, with everyone doing everything the same way. However, issues can arise when the vendor does not have the same understanding of the requirements as you do. As an example, during an attempt to implement a new safety system at a large organization, the vendor was promoting the benefits of a ready-to-use industry-based configured system:

> *"We were supposed to be minimally involved in the requirements, but we had to dictate them almost word for word. We were supposed to do a delta validation, but when we dry-ran the UAT or the core, none were able to complete..."*

As another example, an affordable implementation that leveraged two companies configured within the same platform resulted in an increased budget and longer timeline for a large organization:

> *"We spend two years during which we could not get our own specific how-to in the system because it was supposed to be shared. When we learned the other company was requesting also its own take, we decided to have our own platform or our own data."*

Decisions needs to made about integrating with your current solution, bringing in a new solution, outsourcing or using the cloud. The expectation with outsourcing is that quality will increase, cost will decrease and transparency into the data and outputs will increase. Instead, some companies have found that they have twice the staff for roughly the same number of cases, with lower quality.

> ***"At X, we were told that outsourcing our cases intake and QC will minimize our involvement, allowing us to work exclusively on the medical review, or on complicated cases. As soon as the outsourcer started, we were bombarded with emails and questions about single cases. At the end, our projected costs substantially exceeded all estimates, while our output was only marginally higher."***

When implementing through the cloud, it is expected that each new release will be implemented seamlessly. However, with development on a Windows server, there are some limitations in design, such as limited scalability and upgradability. As an example, one company that chose to adopt a cloud-based safety system discovered later that it was not adaptable to their evolution:

> ***"We had a great experience during implementation. After a while, we wanted to tweak our workflow and certain distribution rules. We were told we could not. We started having to do workarounds because our organization changed. At the end, we had more Excel files used to track what we were doing compared to how we were doing it than even before we switched to this system."***

In addition, the sponsors expect that they will own their data; however, the data might be provided, but not the configuration, which limits the value of those data.

> ***"We wanted to get the data for starting a comprehensive Data Warehouse in R&D. We were told we could get only dumps a certain number of times a year, and without the configuration since it was considered proprietary. The data we got had so little capability to be denormalized that we decided to switch to a different 'cloud' provider in a private dedicated 'cloud.'"***

With each new version, there are also questions to be answered, starting with how frequently, how quickly and which versions you should update. Is additional functionality required, such as R3, IDMP, Embedded CAPA, consolidation or localization? The configuration needs to be stabilized, and the ever-changing rules will need to be validated, documented and in production in time. Other considerations are DSEA requirements, privacy and confidentiality.

Should you assess or bid? Consider how long and how much your team will be involved with an assessment; how long will they be away from their day-to-day activities? For bidding, consider how you will achieve a good understanding of the earned value and return on investment (ROI). How long will it be before you know if you've hit the targets to determine the ROI? For both assessing and bidding, how can you account for agility, or the ability to anticipate what's going to happen tomorrow?

Should you consolidate or break it? Specific considerations here include how to still provide an individualized and consistent user experience if you break it into smaller systems and modules. How can you assure good traceability and centralized management without massive queries and reconciliation? There might need to be different ways to make sure that the same information is brought in at the right time to answer the questions. If you consolidate, how many more systems should you integrate, and with whom? For both options, make sure to determine how you can minimize the cost and complexity of change management, because whatever you're doing today will be different tomorrow. What should you consider as core, and what should you consider as global?

What Does the Future Look Like?

Strategic Initiatives

After all is said and done, how will this change how we operate in the future? Strategic initiatives could include active assessment, sustainable change management, delta validation and offering pharmacovigilance as a service.

Active Assessments enable you to assess your situation without pulling key staff into multiple meetings to answer questions. Instead, you can develop a business case with minimal key staff involvement and a significant number of cases from that provider during the assessment itself. Qualified, skilled staff can evaluate the processing of cases into your system and tell you what you are missing, determine your quality and describe how it can be improved.

Sustainable Change Management can be achieved with small tweaks in the processes and systems. Aligning and maintaining electronic learning, inclusive of your own SOPs, working instructions and typical cases, benefit both internal onboarding as well as the support and services provided by the vendor. New staff can be well trained in certification and providing visibility for service vendors regarding change management.

Delta Validation provides what you need to modify for the next release, from a systems (documentation) perspective and staff involvement, with limited time, effort and cost. It is achieved using your own configuration and case data to automatically evaluate upcoming releases or hot fixes with limited involvement from your staff.

Utilizing **Pharmacovigilance as a Service** provides your organization the full knowledge of the benefit-risks of compounds while taking care of systems, processes and data. It involves co-ownership of certain tasks or decisions depending on the product lifecycle or the progress of global approvals/partnerships. Outsourcing pharmacovigilance provides flexibility in these processes.

Safety Partner and Affiliate Management

The management of your safety partners and affiliates will help ensure that you are meeting all of the obligations in each of the countries in which you are operating, particularly those that are described in legal terms. The mission of a system facilitating this type of management supports the seamless integration and transfer of data across the clinical financial system and safety platform to enable real-time tracking of delivery and payments as the per contractual terms with affiliates and safety partners. The contract management system (e.g., ClinPay) should be able to trace the safety system and data back to the contract, allowing you to determine if you are over- or under-delivering according to your contract. The outcome is better control and management of all contractual engagements, with the clinical financial system implementing the contracts and the safety solution (e.g., Argus, ARISg) handling the reporting and data entry/intake.

SEAMLESS INTEGRATION AND TRANSFER OF DATA ACROSS THE CLINICAL FINANCIAL SOLUTION (CLINPAY) AND SAFETY PLATFORM (ARGUS)

Manage reporting and consolidate with payment terms (contracts) and track data entry/case intake to manage affiliate contract terms.

Intake, case processing and expedited reporting

Case intake from source documents can be expedited using the Optical Character Recognition approach. An intuitive intake approach can help to capture the adverse events that really matter. The use of structured output can ease data entry into any safety solution, which can facilitate data entry.

Case processing services can be integrated with safety systems, using an accelerator-based approach.

Finally, case submissions using an R3 platform (TransformPV) is R3 compliant and can be integrated with existing safety solutions. A plug-n-play solution requires no infrastructure footprint. Moreover, a simultaneous R2-R3 view helps to understand the transformation process.

Aggregate, quality assurance and signal management

For aggregation, the Quadrants warehouse centralizes and integrates organizational global quality processes, which include the management and reporting of quality issues, change control, productivity metrics, compliance metrics and workload metrics. Any reporting and analytics platform with extensible ETLs can be used.

Regarding quality assurance, a quality management platform (e.g., Quadrants) can be used to manage quality issues for ICSRs, periodic reports and signal logs. It can enable identification of quality issues during the case processing lifecycle and facilitate communication with global stakeholders. In this way, quality can be kept in mind in an efficient, proactive way. Organizations are empowered to plan and execute end-of-line quality control activities.

For signal management, the Quadrants extensible alert engine enables organizations to setup alerts and associate those alerts with a comprehensive CAPA workflow.

Application Development Maintenance Operations Services

These services aim to support the patient journey through a clinical trial using patient engagement services and a patient outreach center. They allow you to listen and dialogue with the patient about your product to determine the true benefits, collect real-world data (e.g., adherence, quality of life) and move beyond purely compliance. Patient engagement and compliance improves by leveraging devices, and potentially wearables that connect your applications via App xChange with flexibility and customization, if needed.

Example: Patient engagement from landing page of the clinical trial, keeping engaged beyond the end of the patient journey in the clinical trial (with seamless collection of the data and distribution within the fit to purpose information system)

Clinical Safety

Clinical safety can be improved using any of the following strategies, including an accelerators-based approach to manage the integration of the EDC and safety. An integration approach based on "Data-on-Demand" can also be used, with trigger-based refresh of the tables, custom views, enhanced performance and efficiency and portal page to initiate ad-hoc requests. For managing deletions and disassociations, data can be synced and updated, including deletion of case data (if the data are deleted in Inform). Other strategies include codelist management, custom reporting (difference report with previous, current and accepted database values) and error reporting (configurable alerting service to send automated emails).

Conclusion

There are ways to obtain full and transparent access to the combination of safety expertise, process excellence and systems specialists that will improve your practices, quality, efficiency and compliance in a sustainable and scalable way—even when you feel that the current safety technologies are confusing and there is added scrutiny by your management for costs, efficiencies and increasing collection of adverse events during this time of significant changes.

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About Bioclinica

Bioclinica is a specialty services provider that utilizes expertise and technology to create clarity in the clinical trial process. Bioclinica is divided into three business segments to deliver focused service supporting multifaceted technologies. The Medical Imaging and Biomarkers segment provides medical imaging and cardiac safety services and includes a molecular marker laboratory. The eHealth Solutions segment comprises an eClinical technology platform and professional services along with safety and regulatory solutions. Under the Global Clinical Research segment, Bioclinica offers a network of research sites, patient recruitment/retention services, and a post-approval research division. The company serves more than 400 pharmaceutical, biotechnology, and device organizations – including all of the top 20 – through a network of offices in the U.S., Europe, and Asia.

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