Pharmacovigilance in 2020: Boldly Shaping the Future An overview

Part 2:
Identification of Medicinal Products (IDMP) implementation

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ABSTRACT

Identification of Medicinal Products (IDMP) is a worldwide effort to harmonize medicinal product specifications across regulators and industry as part of continuing efforts towards harmonisation in the pharmaceutical industry. It covers the whole life-cycle of a product from the laboratory onwards. When implemented, IDMP will provide the basis for the unique identification of medicinal products and will facilitate the exchange of information between competent authorities, clinical trial sponsors and marketing authorisation holders (MAH) world-wide.

IDMP is based on a set of five ISO standards published in 2012. These standards establish definitions and concepts describing data elements and their structural relationships that support the full description of any medicinal product worldwide in a structured and unique manner.

The EU is the first region in the world to start the implementation of IDMP. Implementation is following a phased approach. A major phase has already started, as EMA initiated the process of standardising organisation data i.e. organisation name and location address for relevant stakeholders such as MAHs, sponsors, regulatory authorities, manufacturers and CROs as well as referential data i.e. standard lists of terms such as catalogues of dosage forms, units of measurement, and routes of administration.

IDMP implementation will require significant effort particularly from the competent authorities, but also from MAHs, clinical trial sponsors, manufacturers, CROs and other stakeholders.

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INTRODUCTION

International exchange of safety data is an established process that helps stakeholders enrich their safety database and increase their ability to monitor the safety of pharmaceutical products. However, lack of homogeneity is a major limiting factor in the usability of safety data from different countries/regions. In order to overcome this, in 1997, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed an international standard for the structure of safety data relating to individual patients. This standard, which is coded as ICH E2B, has been updated twice, with the last update, ICH E2B (R3), being ~~published in 2011~~. The updates addressed certain issues that came up during the experience with worldwide safety information exchange. In particular, exchange of information between organisations in different geographical areas revealed the inconsistency of data elements in various regions of the world. Striking examples are differences in active substance naming, measuring units or description of dosing.

The enhancements achieved by ICH E2B (R3) would be limited without a common standard for medicinal product identification. Following several consultations, the stakeholders agreed on a solution that could overcome existing variations and national boundaries. This solution necessitated the use of a common standard that regulates internationally all conceivable characteristics of medicinal products. ISO, the most prominent international standardization organisation was chosen to issue this standard. The technical specifications for such a complex and demanding project took into account existing knowledge, know-how and standards to identify a starting point. The best platform identified was the HL7 standards that support the exchange, integration, sharing, and retrieval of electronic health information. These existing and widely used standards among health care provision organisations define how information is packaged and communicated from one party to another, setting the language, structure and data types required for seamless integration between systems. IDMP has built on this platform to develop standards appropriate to the characteristics of medicinal products.

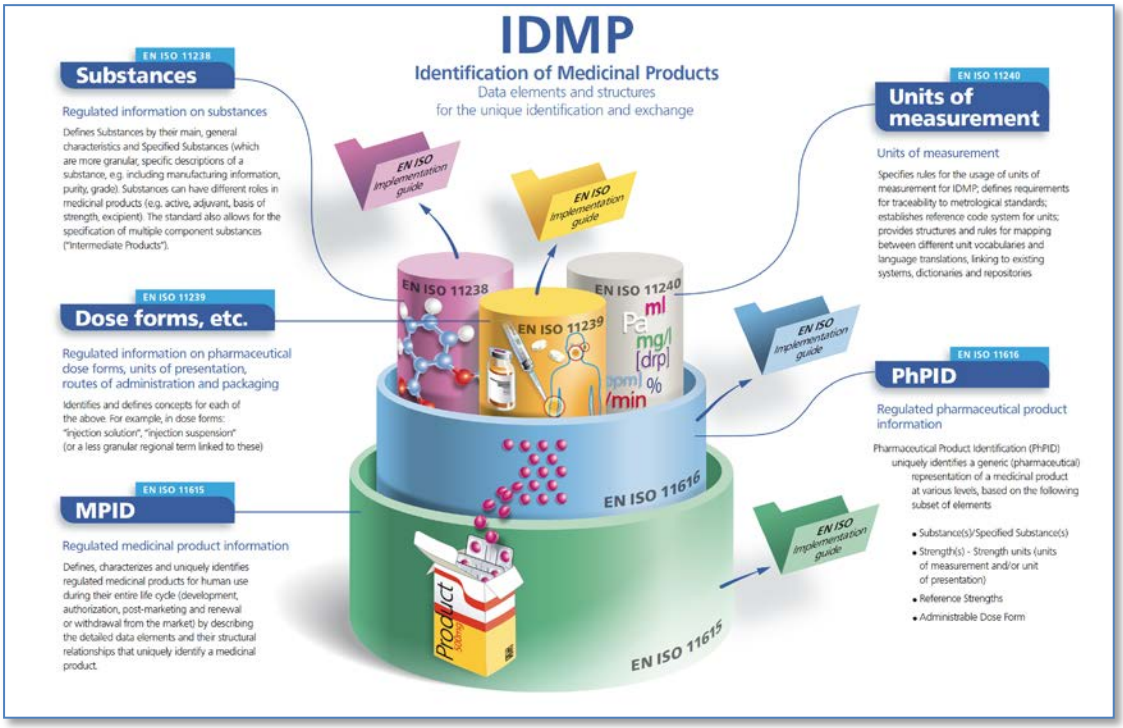
HL7 *"Founded in 1987, Health Level Seven International (HL7) is a not-for-profit, ANSI-accredited standards developing organisation dedicated to providing a comprehensive framework and related standards for the exchange, integration, sharing, and retrieval of electronic health information that supports clinical practice and the management, delivery and evaluation of health services."*

What is IDMP?

IDMP is the set of 5 ISO standards that are based on the HL7 standards for data elements, formats and terminologies to uniquely identify and exchange information on medicines. Each standard describes different distinct elements of a pharmaceutical product. A medicinal product is understood as a unit characterised by the following distinct elements:

- Element 1 is **substances**. Active and inactive, along with all their characteristics such as manufacturing information, purity, isotope, etc. This is regulated by **ISO 11238**.
- Element 2 consists of (a) **dose forms** such as cutaneous patch, ear spray or eye drops, (b) **units of presentation**, such as ampule, drop or puff, (c) routes of administration such as oral, nasal, cutaneous, and (d) packaging such as blister, box or prefilled syringe. This is regulated by **ISO 11239**.
- Element 3 is **units of measurement**. This is an extremely important tool for information exchange, as units of measurement vary considerably among different countries. It specifies rules for the usage of units of measurement, establishes reference code system for units and provides structures and rules for mapping between different unit vocabularies and language translations. This is regulated by **ISO 11240**.
- Element 4 is **pharmaceutical product information**. This allows the unique identification of a pharmaceutical product in its generic form consisting of its parts as mentioned above (substances, dose forms, units of presentation, routes of administration, packaging and units of measurement). This subunit brings together all information that make up a pharmaceutical product (parts and interrelations) without regulatory information i.e. medicinal product name or marketing authorisation type. This is regulated by **ISO 11616**.
- Element 5 is **medicinal product information** such as medicinal product name, marketing authorisation number, date of product renewal. This is regulated by **ISO 11615**.

The following figure provides a schematic with an easy to understand illustration of the 5 different elements described by the corresponding ISO standards:



Source: ISO TC 215, Working Group 6 (Pharmacy and Medicines Business), December 2014

Scope Widening

Although, as described above, ISO IDMP evolved as a tool for improving pharmacovigilance activities, competent authorities gradually recognised that using an internationally harmonised approach to identifying and describing the medicinal products, has a much wider usefulness than improving the outcome of pharmacovigilance activities.

In an EMA[1] publication on this issue, the following additional benefits are expected as a result of IDMP adoption:

- facilitating the identification and exchange of product and substance information globally, across regulators;
- improving data integrity and reliability;
- enabling reuse of data across different procedures and regulators;
- reducing silos and improving interoperability across EU systems through the optimisation and simplification of data operating models and data management practices;
- streamlining, optimising and simplifying regulatory processes to fulfil regulatory requirements more efficiently;

[1] Introduction to ISO Identification of Medicinal Products, Information Management Division, SPOR programme, 29 November 2016, EMA/732656/2015

- speeding up decision-making and improving communication with the stakeholders through easily accessible and highly reliable data.

The list below, refers to practical aspects of the benefit expected:

- support of cross - border electronic prescriptions of medicines
- increase efficiency in identifying counterfeit medicines
- faster response to address shortages
- faster product identification in case of withdrawal of products with the same active substance
- quicker and more efficient response to findings on manufacturing sites that have impact on the quality of products
- minimise incidences of repeat information submission to authorities in the context of regulatory applications

PRACTICAL IMPLEMENTATION OF IDMP IN THE EU

Although IDMP shall support information exchange worldwide, its implementation is region dependent. The EU is the first region to start implementing the IDMP. EMA's approach to implementing the ISO IDMP standards is based on four domains of master data in pharmaceutical regulatory processes: Substance, Product, Organisation and Referential data (SPOR). Although there is no direct mapping between the four SPOR domains and the five IDMP ISO standards, SPOR data elements will cover all requirements of IDMP. The four SPOR domains are:

- **Substance data**: medicinal products' ingredients and materials. Substance data will be sourced from the current EudraVigilance medicinal products database (Human Art. 57 database - xEVMPD). As the ISO IDMP standard requires additional data attributes as those currently required by xEVMPD, the EMA is currently in the process of enriching this data with the support of marketing authorisation holders. This corresponds to ISO 11238;

  > ***Human Art. 57 database - xEVMPD*** *is EMA's medicinal product dictionary aiming at creating a list of all medicines authorised in the EU, to identify medicines accurately (especially those included in reports of suspected adverse reactions), and to co-ordinate the regulation and safety monitoring of medicines across the EU.*

- **Product data**: medicinal products' regulatory information (e.g. marketing authorisation, packaging and product information). Product data will be provided based on data sourced from xEVMPD and SIAMED (EMA's database containing regulatory information for products authorised by the centralised procedure). This corresponds to ISO 11615 and ISO 11616;
- **Organisation data**: data comprising organisations (e.g. name, address, type of organisation) for relevant organisations such as MAHs, sponsors, competent authorities, manufacturers, CROs. Organisation data will be made available by means of a dictionary of organisations. This relates but does not correspond to ISO 11615;

- **Referential data**: lists of terms (controlled vocabularies) to describe attributes of products, e.g. lists of dosage forms, units of measurement and routes of administration. EMA will host existing reference lists from different maintenance organisations (WHO, EDQM, MSSO, BfArM, etc). EMA will be a maintenance organisation for new lists where no maintenance organisation exists; This corresponds to ISO 11239 and ISO 11240;

Common for all SPOR data elements is that:

- required translations will be done by national competent authorities of EU member states;
- industry and other parties will have to request registration of terms before regulatory submission;
- all organisations need to register legacy & specific terms with EMA.

What is expected from the Industry?

Although IDMP implementation is complex and far-reaching, the competent authorities, i.e. the EMA in the case of the EU will provide the main deliverables. However, a lot of effort is still required from the industry, in the sense that, all the data available to an organisation that are associated with medicinal products should be identified, re-structured, organised, and finally streamlined with the standard definitions, as they become available/published.

In this context and since IDMP implementation will require the handling, submission and maintenance of more data than is currently requested by xEVMPD, organisations will also need to identify this additional data, that will most probably be sourced from existing company systems, such as marketing authorisation information held in various locations.

In case of non-existing data, or discrepancies, change requests need to be made via a new user interface, which triggers an evaluation process. In such cases, provisional terms may be provided in the meantime until more comprehensive evaluation can be performed.

General Process Steps

IDMP implementation should be handled as any other project involving structured process steps. Ideally each organisation shall proceed as follows:

- Identification of data sources, such as authorisation dossiers, manufacturing sites, xEVMPD, company databases such as regulatory information management systems, excel spreadsheets, agreements with external partners (contract manufacturers, CROs etc.), internal unstructured sources in clinical development, regulatory or pharmacovigilance departments in the form of stand-alone paper and electronic documents;
- identification of relevant data from the sources mentioned above;
- data review including QC;
- data completion, if missing;
- standardisation of data using standard company terms, even in the absence of standard terms from the EMA.

The challenge for a successful IDMP implementation is that following the standardisation of data naming conventions by the competent authorities the corresponding company data that exists in various forms and various locations throughout the world should be checked against these standards, and if needed, updated, modified or added. Therefore, a key element for a successful IDMP project is a comprehensive data source identification.

Expectations per each SPOR domain

With respect to each of the SPOR domains, the following is expected by the Industry:

Substances

EMA will provide a dictionary of substances based on internationally harmonised definitions that will be available from a single source and will be able to interoperate with other systems used in performance of regulatory activities.

Industry will need to update their own substance terminologies used for the EU-wide submissions including xEVMPD. This means that all data/information containing substances shall be identified throughout the whole organisation and "tagged" in order to be checked against the standard term when it becomes available. Additionally, instances of multiple substance name variants and translations in various languages shall be cleaned up as a preparatory action. The substance terminology of the products shall be granular enough to identify scientifically relevant aspects of each substance.

Products

Product information shall be identified throughout the organisation, analysed and completed if needed. Various departments will be expected to provide information about relevant product information such as administrable dose form, unit of presentation, route of administration, device type (if combined medical device advanced therapy medicinal products-ATMP) or device trade name (if combined medical device ATMP), or clinical particulars. Expertise in coding systems such as MedDRA or ATC will be required.

Organisations

One of the first two SPOR implementation areas is Organisations. EMA's aim is to build a single, clean and consolidated repository within the EMA, with organisation identifiers. This repository will be in the Organisations Management Services dictionary (OMS dictionary) a dictionary with structured and standardised organisation data, which will support IDMP implementation.

The industry shall start identifying all elements that compile their organisation throughout all parts of their structure worldwide. Complete organisation information along with interrelations with other organisations shall be identified and managed. As soon as the OMS dictionary becomes available, existing data shall be reviewed and updated and if needed completed.

As individuals in important roles (e.g. EU QPPV) shall be associated with organisations, personnel titles and job descriptions shall be streamlined. Equally, associations with important

vendors shall be identified and correctly assigned including correct terminology. Several naming conventions with vendors that still carry "historical" terminology shall be updated and streamlined.

Organisation data will be integrated in all four electronic application forms for all address fields in the EMA electronic submission system (eAF). Use of organisation data in the eAF will initially be optional. ~~Applicants are advised~~ to perform a search from within the form to familiarise themselves with the use of organisation data and to ensure that they are familiar with the process before its use becomes mandatory.

OMS dictionary is planned to be completed and published by Q3 2018. Following publication, MAHs will be requested to check their data against the OMS dictionary data and submit organisation data change, if needed.

Additional Organisation data to be published in the future and the prioritisation of their inclusion in the OMS dictionary are the following:

- Veterinary MAHs for NAPs;
- Contract Research Organisations (CROs);
- Clinical trials sites;
- Academia;
- Hospitals;
- Wholesale distributers;
- MAA/MAH and manufacturers in the context of herbal and homeopathic medicinal products or compassionate use medicinal products;
- QPPV (Qualified Person for Pharmacovigilance)

Referentials

The EMA will provide a single, trusted source of referential data to be used across the EU regulatory network and the pharmaceutical industry, with consistent mechanisms to update referentials lists.

Identified data will have to be, checked and harmonized with the data provided by EMA via the single source for referential data for all stakeholders. The industry shall identify and resolve data quality issues in referentials. Identifying and managing all this information will impact the entire organization. Specifically, in organisations where, due to the XEVMPD population, pharmacovigilance is involved in this process, there will be substantial involvement of the pharmacovigilance department. Concerned departments at both the headquarters and the affiliates as well as service providers shall be involved in data management responsibilities of referential data.

In further detail, a number of steps to be performed as part of the preparatory phase of referentials implementation, are as follows:

- Standardise any free text package descriptions, using the terms available in the Containers list from EDQM
- Map local containers' data (incl. standardised package descriptions) against existing container lists
- Update local referential data against existing lists, such as pharmaceutical dose forms, routes of administration, units of measurement etc.
- Map local data against new Referentials lists, such as materials as they become available
- Submit requests for new/updated Referentials terms prior to submitting applications (pre-registration)
- Keep local referential data synchronised with standard referential terms as they become available

> ***EDQM*** *(European Directorate for the Quality of Medicines & HealthCare) is a Directorate of the Council of Europe that traces its origins and statutes to the Convention on the Elaboration of a European Pharmacopoeia. Among other responsibilities, EDQM is setting quality specifications and pharmaceutical reference standards.*

Current Status

EMA has done substantial background work on IDMP implementation. It is expected that prior to the mandatory implementation in a given regulatory business process, there will be enough time for the stakeholders to get prepared. IDMP implementation will require major changes for stakeholders. Each organisation is going to have to design new processes about updating and completing its relevant data and communicating updated data to agencies.

Mandatory implementation will start with Organisations. It will mean that all submitted data must be completely in line with the standards but the current known data submission process will mostly remain unchanged.

Timing of implementation

As per the implementation history of projects of this magnitude, any time projection is subject to possible extensions. Being a very complicated issue, timelines no matter how largely calculated, may not be kept. However, EMA has started and is already intensively working on it and it will definitely carry on fast.

In the EU, submissions of ~~IDMP data~~ will become mandatory most probably by the end of 2018 or beginning 2019. FDA is currently working internally on IDMP and is expected to follow with legislative initiatives shortly thereafter. Upon publication of the legislation by the FDA, MAHs will have 24 months to be prepared until legislation becomes effective. PMDA Japan is expected to join IDMP sometime in the future. However currently there are no published time schedules.

CONCLUSION

Stakeholders shall see IDMP as an opportunity for structuring and better organising their product related data. If stakeholders take advantage of the data uniformity that will span from each single MAH or service provider to the major competent authorities worldwide, they will realise that an initial investment in adapting to IDMP, will offer multiple benefits. IDMP is a case where the competent authorities will have to provide a lot of deliverables that can help stakeholders benefit through standardisation as long as they fully implement IDMP throughout the whole organisation. Regulatory compliance is the least benefit of a consistent and quick implementation of IDMP. The major benefit will be to have all product data organized in a way that will be the basis for every possible use in the company.

The decision of EMA to start with the least complicated area will allow all stakeholders to jump into the matter and gain experience with an area that is very well known, simple and has only a few elements. This will enable all stakeholders to assign responsibilities and allow the personnel to learn on an easy task. However, this is not enough for the industry to be prepared for IDMP implementation.

Organisations should be trying to familiarise themselves with IDMP and starting to think about the resources they will need to identify, manage and conform their data with IDMP standards.