Identifiers to Enable Pharmaceutical Quality Knowledge Management (PQ KM) – a Progress Report

Background and Rationale

As pointed out in the 2022 Joint Reflection Paper (JRP), effectively managing changes to pharmaceutical manufacturing processes is challenging, especially to the marketing authorization holders (MAH) submitting the same dossier to multiple regions. Different formats and contents in the dossier are expected due to the country/region specific conventions and legal/regulatory expectations. Such inconsistencies also cause inefficiency amongst regulators and hamper mutual reliance efforts to share knowledge amongst regulators and facilities to be more nimble, agile in regulatory decision making. The envisioned PQ KM system aims at strengthening international collaboration to support global development, manufacture, and supply of pharmaceutical and biological/biotechnological medicinal products.

One key challenge to international collaboration stems from how to identify or confirm that it is the same product under assessment by different national regulatory agencies (NRA) in parallel or at different times. Solving this challenge would allow NRAs to effectively collaborate or share their assessment outcomes and decisions, and eventually make the same product available to the patients in multiple regions sooner. Although some authorities use national or regional identifiers, a common and interoperable limited set of identifiers for manufacturing facilities, pharmaceutical products, substances, marketing applications, and/or marketing application holders is not currently endorsed.

Purpose and Approach:

Recognizing the above challenge, the JRP called for a cross-organization collaboration on defining identifiers. Subject matter experts from the ICMRA/IPRP/ICH/PIC/S member agencies were convened to form a working group. The group is tasked with considering the status of current standards, their implementation, the potential need for new standards and approaches for the development, adoption, operation, governance, and maintenance of a limited set of internationally harmonized identifiers related to pharmaceutical products and the establishments that manufacture them.

In the development phase, the group focused on the key quality information in the eCTD Module 3, and examined the current practices in different NRAs (e.g., EMA, HPRA, PMDA and USFDA) and existing standards and initiatives, such as:

- Key organization information and quality attributes to identify the same product
- The ISO IDMP standards (11615, 11616, and 11238) in identifying medicinal products, pharmaceutical products and substances
- The Substance, Product, Organization and Referential (SPOR) Data Management Services from the EMA
- The Global Substance Registration System (G-SRS) (which provides common unique identifiers (UNII) for all the substances)
- The PIC/S recommendation for unique facility identifiers

The above effort resulted in a proposed identifiers framework, which should help NRAs to quickly confirm the same drug product is under assessment to accelerate or better enable global collaboration and mutual reliance.

Outcome and Discussion:

This framework, as proposed, contains two tiers of identifiers:

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- Primary identifiers (in Appendix 1) are key information about the drug substance and product, and the associated organizations (e.g., MAH and manufacturers). Such information is currently mandatory and submitted in dossiers, typically using well formulated terms or codes in highly structured format. They can be easily located in the submissions (e.g., the cover letter or application form) to serve as effective identifiers. It is estimated that the use of these the primary identifiers should give the NRAs high confidence in determining product "sameness".
- Secondary identifiers (in Appendix 2) are additional and more granular information about drug substances and products, and associated organizations. Using these identifiers will give a higher level of confidence in determining product "sameness"; however, it may take significantly more effort because they are typically text-based and deeply "buried" in submissions. Therefore, these may be less effective as identifiers.

Regarding the primary identifiers, the work group has a high level of consensus on what the limited set of primary identifiers should be. Also majority of them have been well defined in ISO 11615/11616/11238, which would support their adoption. In fact, these identifiers have been widely and effectively used by different NRAs following their own conventions and practices, including different controlled terms and system generated codes. For instance, FEI and DUNS codes are used by the USFDA to identify manufacturing establishments; however, using such codes is not required by the PMDA. EU/EEA NRAs and EMA use a service called "Organisation Management Service (OMS)" that supports EU regulatory activities and business processes; it stores master data comprising organisation name and location address for organisations such as MAHs, sponsors, regulatory authorities and manufacturers. For application types, different NRAs have different formats due to the respective regional requirements. For dosage form, there is no internationally agreed-upon list of controlled terms. Consequently, the same product can still be labelled differently using the proposed framework, compromising the interoperability of these identifiers across NRAs. Therefore, the successful use of these identifiers for reliance is contingent upon the eventual adoption of internationally recognized and controlled terms or codes.

The group sees the opportunities in both the ongoing and upcoming ICH efforts. The ICH M4Q under revision can clearly specify these identifiers as mandatory for all future submissions and prescribe the desired locations. In addition, the Structured Product Quality Submission (SPQS) effort that will be undertaken in ICH can further harmonize submission content (i.e., data elements and format) and the associated conventions (e.g., the controlled terms and coding strategies). Their implementation and adoption will greatly accelerate the usage of these identifiers; for instance, SPQS can prescribe that all the identifiers are captured in a specific section of a well-structured submission form. To enable such a vision, the Global IDMP working group (GIDWG), formed in 2021, is leading to the establishment of a framework for the global implementation of the ISO IDMP standards and maintenance of global identifiers.

Regarding the next steps for the working group, a deeper dive into the practices and conventions currently used by different NRAs may be insightful to determine the specific differences and potential approaches to harmonize the format/content of these identifiers, to enhance interoperability. The results from this exercise can also serve as a critical reference especially for the upcoming ICH SPQS effort.

Key references:

1. The 2022 PQ KMS Joint Reflection Paper
2. Considerations on use of unique identifiers to enable reliance through a global regulatory PQ KMS
3. EMA PMS ISO IDMP Implementation Guide Chapter 8 Practical example (July 2022)

4. ISO 11238: Data elements and structures for unique identification and exchange of regulated information on Substances
5. ISO 11239: Data elements and structures for unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging
6. ISO 11240: Data elements and structures for unique identification and exchange of units of measurement
7. ISO 11616: Data elements and structures for unique identification and exchange of regulated pharmaceutical Product information
8. ISO 11615: Data elements and structures for unique identification and exchange of regulated medicinal Product information

Appendix 1: Primary Identifiers

Identifier Name	Rationale	Regulatory Note
Drug Substance Related Identifiers		
Drug Substance Name	A key identifier to determine the same product	Currently available naming convention include International Non-proprietary Names (INN) and IUPAC names, and CAS Registry Number (CAS RN). Also available is the GSRS Unique Identifiers (UNII, combo of numbers and characters). EMA assigns SMS ID, using as a combination of numbers. Although there is no harmonization of the identifier at the global level, GIDWG has demonstrated at ISO TC215 WG6 and other venues business rules conforming to the ISO IDMP 11238 standard to achieve global harmonization between NRAs.
Active Substance Master File (ASMF) / Drug Master File (DMF) Holder Name & Address	This is critical because different holders or manufactures may use different synthetic routes, which may bear different risk profiles (thus different level of quality assessment effort).	EMA's PMS includes Org and Loc IDs.
Manufacturing Site Identifier, Name and Address	This identifies the specific drug substance manufacturer. Based on the identifier code, the name and address can be further identified (see Secondary Identifiers)	Currently used identifiers include FEI, DUNS, Geocoordinates mainly by the EMA and USFDA. From an EMA perspective, identification in the OMS system uses Org and Loc IDs.
Drug Product Related Identifiers		
Marketing Authorization Holder (MAH) Name & Address	Identify the application owner.	EMA's PMS assigns Org/Loc IDs, using a combination of numbers.
Application Type	Identify the type of products/application (e.g., biologics, innovator or generic drugs).	This is regulator specific currently. USFDA uses NDA/ANDA/BLA + 6-digit number. EMA's RMS capture application type IDs, as combination of numbers. Potentially to establish an international standard/practice to capture key basics (e.g., Legal basis + Large/Small molecule + Numbers).
Dosage Form (IDMP standards use Dose Form)	The same MAH may have different dosage forms for the same drug substance.	In general, controlled terms are used by different NRAs but not harmonized. USFDA has controlled terms and concept codes for commonly seen dosage forms via NCI EVS.

Identifier Name	Rationale	Regulatory Note
		EMA's RMS has dose form IDs (codes) for different dose forms (EDQM as the owner). Although there is no harmonization at the global level, GIDWG has demonstrated at ISO TC215 WG6 and other venues business rules conforming to the ISO IDMP 11239 standard to achieve global harmonization between NRAs across different terminologies.
Route of Administration (ROA)	Different route of administration may warrant different level of scrutiny during the quality assessment.	USFDA has controlled terms and concept codes for commonly seen ROAs via NCI EVS. EMA's RMS has Routes and Methods of Administration terms and IDs (EDQM ownership) in the RMS.
Indication	Different indications (including target population) may lead to different risk-benefit profiles, which may warrant different level of scrutiny during the quality assessment.	EMA's RMS has Medical Dictionary For Regulatory Activities list (MedDRA)(MSSO ownership). USFDA uses SNOMED for indication.
Manufacturing Site Identifier, Name, and Address	This identifies the specific drug substance manufacturer. Based on the identifier code, the name and address can be further identified (see Secondary Identifiers).	Currently used identifiers include FEI, DUNS, and Geocoordinates mainly by the EMA and U.S. FDA. Advocate for Geocoordinates to be internationally used in submissions. From an EMA perspective, identification in the OMS system uses Org and Loc IDs also captures the name and address.
Profile Class Codes	Reflects Product classes produced by the site and is updated during the inspections.	EMA: During MRA process, PCC used by USFDA and EU nomenclature used on GMP certs and listed in Eudralex was mapped.
Unit of Presentation	Identify the final delivery format of the drug product. Certain final delivery format may warrant additional level of scrutiny during the quality assessment.	It is a discrete field in IDMP. USFDA: this is typically imbedded in or implied by the finished product name.

Appendix 2: Secondary Identifiers

Identifier Name	Rationale	Regulatory Note
Drug Substance Related Identifiers		
Active Substance Master File (ASMF) / Drug Master File (DMF) Number & Version Number	To further help triangulate the drug substance manufacturer.	Assigned by the regulators; but different formats used are in different countries. The version number is typically generated by the ASMF/DMF holder and critical to determine the same version of a given ASMF/DMF is being assessed by regulators for mutual reliance.
Synthetic Route Description	(Optional) In principle, different synthetic routes may result in different impurity profiles and hence safety concerns.	This is not an efficient identifier to quickly triangulate the drug substance/product. A global IT effort to render the same CMC/CMC PAC package to multiple regulators is more effective than using this as an ID.
Stability Specification	(Optional) In principle, the same drug substance from different manufacturers or DMF holders may have different specification.	Same as above.
Drug Product Related Identifiers		
Application Number (Marketing Authorization Number)	In conjunction with the Application Type (primary ID) to identify the drug product.	Currently regulator specific regarding its format (e.g., 6-digit number for USFDA)
Drug Product Name (established)	Identify the product using commonly known non-proprietary (established) name.	Naming convention is different for different regulators.
Strength	This identifier can be critical for PAC as some PACs are only intended for certain strength under the same market authorization (application)	IDMP can help address this need. Although there is no harmonization at the global level, GIDWG has demonstrated at ISO TC215 WG6 and other venues business rules conforming to the ISO IDMP 11240 standard to achieve global harmonization between NRAs.
Packaging Configuration	Different packaging configurations may result in different unit operations and stability considerations (e.g., blister pack vs. bottle vs. pharmacy bulk pack). From the quality assessment perspective, this aspect is critical.	May not be a stable identifier as it may change (due to PACs) throughout the product lifecycle. IDMP can help address this need.
Sterile or non-sterile	Help to identify if sterile processing is involved or not. If sterile, additional	Currently not captured in a structured way in most countries. It may not be an efficient identifier.

Identifier Name	Rationale	Regulatory Note
	scrutiny during the quality assessment is warranted.	
Component & Composition	Ensure sameness of formulation (or allows discussion of insignificance of differences like flavours, colours, etc);	In general, this should not be an identifier. However, this is the level or granularity of "sameness" should be defined. In other words, what kind of differences are insignificant (and still consider the finished product being the "same") from the quality assessment perspective.
Product Design (especially for solids-based drug products)	This can be critical for certain product types. For instance, the same drug substance can be formulated into extended release tablets using different release control mechanisms (e.g., matrix-based or osmotic-pump controlled). Such difference will result in different manufacturing process and process controls, which are critical to quality assessment.	Same as above.
Specifications	(Optional) In principle, the same drug substance from different manufacturers or DMF holders may have different specification.	This is not an efficient ID to quickly triangulate the drug substance/product. A global IT effort to render the same CMC/CMC PAC package to multiple regulators is more effective than using this as an ID.
Manufacturing process (e.g., flow diagram, and critical process parameters)	Such details are important to quality assessment.	Too granular to be an effective identifier.