Global IDMP PhPID End-to-End Testing

Global IDMP Working Group

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1. Introduction

1.1 Identification of Medicinal Products (IDMP)

IDMP provides an international framework to uniquely identify and describe medicinal products with consistent documentation and terminologies, facilitating the exchange of product information among regulators, manufacturers, suppliers, and distributors. Once globally implemented, these standards will enhance pharmacovigilance, address drug shortages, and ensure medicinal product safety worldwide. Central to this framework is the Pharmaceutical Product Identification (PhPID), generated by combining a substance's ID, strength, and dose form attributes (including basic dose form, administration method, intended site, and release characteristics).

The global, unambiguous identification of medicinal products is important for achieving international public health objectives, including pharmacovigilance, medicinal product traceability, and pharmaceutical quality.

1.2 Global IDMP Working Group

Following a 2019 WHO workshop on IDMP, the Global IDMP Working Group (GIDWG) was established and chartered. This international group is tasked with conducting and reporting on projects to implement ISO IDMP standards globally and maintain global identifiers and systems. Founding members include the European Medicines Agency (EMA), the U.S. Food & Drug Administration (U.S.FDA), and Uppsala Monitoring Centre (UMC). Regulatory members include the Brazilian Health Surveillance Agency (ANVISA), Health Canada (HC), Norwegian Medicines Agency (NoMA), Saudi Food and Drug Authority (SFDA), and Swissmedic. Industry is represented by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

Contributors include the European Directorate for the Quality of Medicines & Healthcare (EDQM), the U.S. National Cancer Institute Enterprise Vocabulary Services (NCI EVS), and the World Health Organization (WHO). The GIDWG also collaborates with International Standards Organisation (ISO) Technical Committee 215 Working Group 6 (ISO WG 6) and HL7 to propose, test, and report solutions addressing issues hindering regulatory implementation of IDMP standards.

In 2022, following Recommendations from the 2019 WHO workshop, the GIDWG initiated five projects aimed at identifying and developing consensus on processes, best practices, and operating models for maintaining global identifiers for marketed medicinal products. These projects also sought to demonstrate how the IDMP standards could be implemented globally to enhance public health safety. The goals across the five projects were to:

- Define and harmonize global medical information for substance identification, dose form identification, and strength definitions.
- Develop the operating model for global PhPIDs, including business rules and a framework for maintaining global identifiers.
- Participate in the development, verification, international review, and acceptance of HL7 Fast Healthcare Interoperability Resources (FHIR) to exchange medicinal product and substance information effectively.

2. Objectives of the End-to-End Testing

The primary objective of the end-to-end testing was to comprehensively assess the readiness of the Global PhPID Service Operating Model across technical, operational, and business dimensions. The assessment involved both load testing, simulating typical daily usage scenarios, and stress testing, pushing the system to its limits with challenging substances and dose forms to validate robustness under future demands.

This report evaluates the operating model's readiness for deployment, emphasizing software functionality, interoperability, processes, and business rules. It also identifies areas for improvement and provides actionable recommendations to enhance performance. Furthermore, the end-to-end testing simulated real-world scenarios for three global IDMP use cases: Pharmacovigilance, Drug Shortages, and Cross-border Healthcare.

The service was designed to generate global PhPIDs for marketed medicinal products. The end-to-end testing focused on:

- Receiving medicinal product information through UMC's PhPID Requestor application from five regulatory agencies (ANVISA, EMA, Health Canada, Swissmedic, and the U.S. FDA).
- Harmonizing this information, generating PhPIDs for marketed products according to GIDWG business rules, and publishing these PhPIDs in the PhPID Publish and WHODrug Insight applications.

3. Global PhPID Service Operating Model

Global PhPID Service operating model is based on the following:

3.1 Value Proposition:

The Global PhPID Service aims to standardize the identification of pharmaceutical products and substances on a global scale. Its objective is to create a unified, structured set of definitions to improve clarity and efficiency in communications about medicines, providing greater certainty to patients.

3.2 Customer Segments:

- Regulatory bodies
- Pharmaceutical industry
- Healthcare professionals

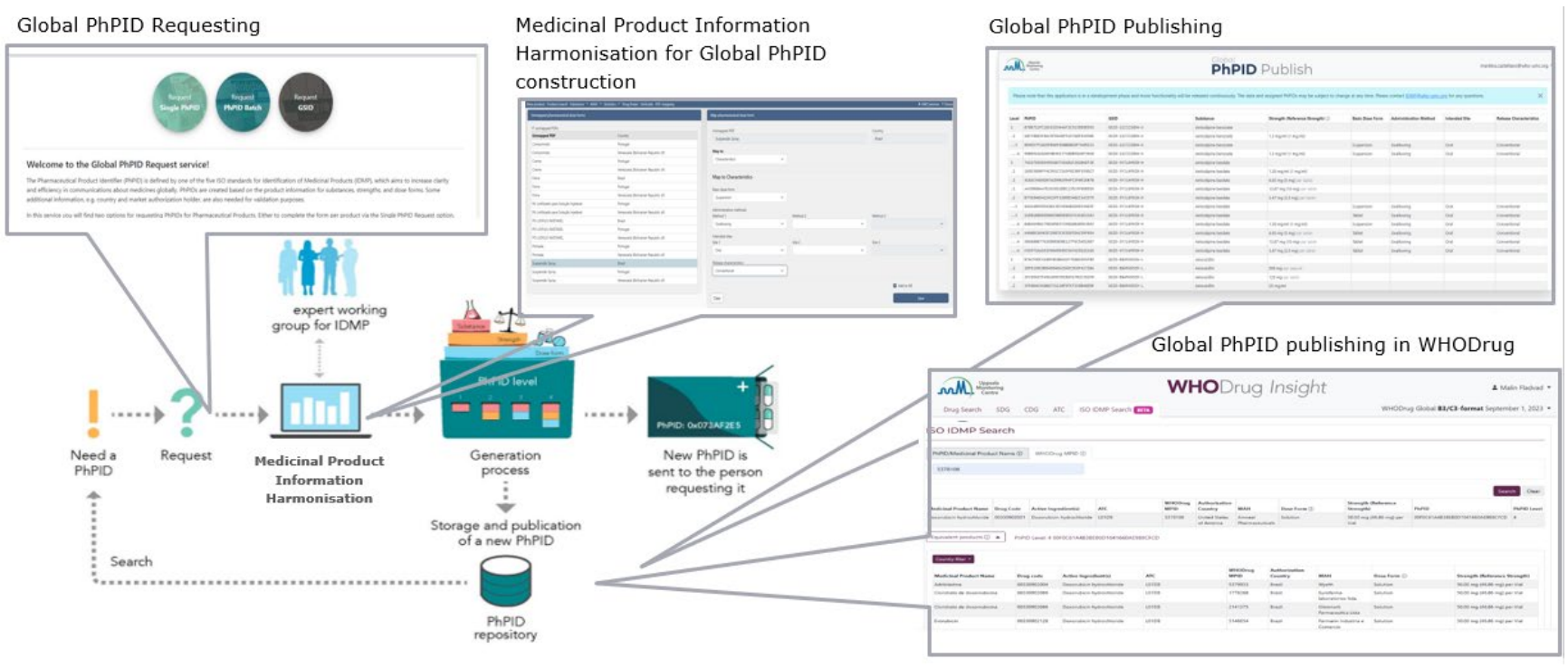


Figure 1: Service Design

3.3 Core Processes:

The Service Design, as illustrated in Figure 1, follows these key steps:

- **Requesting PhPID:** To obtain a global PhPID, medicinal product information must be submitted via dedicated API or via the PhPID Requestor application, either completing a form per product (Single PhPID Request) or uploading multiple PhPID requests (Batch Request).

- **Processing Information:** PhPIDs are generated based on the product information for substances, strengths, and dose forms. Additional information, such as the country and market authorization holder, are also required to verify information relevant to the PhPID. Processing involves assigning Global Substance Identifiers (GSIDs) and harmonizing pharmaceutical product data to generate PhPIDs.
  - **Assigning GSID**:
    This involves assigning a Global Substance Identifier (GSID) at the substance level or, if necessary, at the SSG1 level. The correct GSID is then selected for PhPID generation.

  - **Harmonization of Marketed Pharmaceutical Product Data**:
    This step includes identifying the active ingredient of the product and describing the dose form. Dose form characteristics include release characteristics (RCA), intended site (ISI), administration method (AME), and basic administrable dose form (BDF). These characteristics are indexed for global IDMP and used in generating the Global PhPID. The strength of the product is also defined, including whether it should be expressed as presentation strength or concentration strength. Typically, the strength used for PhPID generation is that of the active ingredient, as indicated in the SmPC. This strength is either entered directly (when the strength indicated in the SmPC is for the active ingredient) or calculated from the base strength (as in cases where the base strength is the strength indicated in the SmPC and the active ingredient is a salt).

- **Generating PhPID:**
  PhPIDs are generated using an MD5 Hash algorithm with a specific input string format:
  - **Identifiers** are separated by a semicolon (;).
  - **Substances** are ordered by GSID and separated by a pipe (|).
  - **Strength & Units**:
    - Amounts are represented with a decimal point (.) and two decimal places.
    - Either presentation strength or concentration strength is used, depending on business rules.
    - Units are defined by the Unified Code for Units of Measure (UCUM) where available. If no UCUM unit is defined, alternative units are used based on a dedicated set of business rules. The units are then translated into a numeric code for PhPID generation.

  - **Dose Form:**
    - Represented by BDF, AME, ISI, and RCA from the European Directorate for the Quality of Medicines (EDQM).
    - Multiple AME and ISI entries are enclosed in square brackets ([ ]) and ordered by ID, from lowest to highest.

- **Publishing PhPID :**
  Once generated, PhPIDs are published in PhPID Publish and WHODrug applications.

3.4 Supporting Processes:

The service aligns with global needs and addresses challenges through the International IDMP Subject Matter Experts (IDMP SMEs) Group.

Organizational Structure:

- **UMC:**
  - **Technical Support:** Responsible for the maintenance and operation of the Global PhPID systems.

- **PhPID Generation:** IDMP Experts handle the processing and harmonization of medicinal product information to generate PhPIDs.

- **GIDWG:**
  - **Global IDMP SMEs Group:** Ensures that the PhPID construction aligns with global IDMP requirements and oversees the business rules for generating PhPIDs.

- **Governance:**
  - **Governance Mechanisms:** Implement governance structures to oversee service delivery and ensure alignment with global IDMP implementation goals.

4. Methodology

The methodology for the end-to-end testing followed a structured process, designed to ensure comprehensive evaluation of the Global PhPID Service Operating Model. Figure 2 outlines the key steps, which included:

1. **Preparation of the Substance Set:**
   A comprehensive Substance Set was created, consisting of 150 substances (350 including variations), encompassing chemicals, nucleic acids, proteins, polymers, and structurally diverse substances. This set was designed to address challenges and issues identified in previous pilot studies regarding substances.

2. **Distribution of the Substance Set:**
   The Substance Set was provided to five regulatory agencies, with each agency having a designated point of contact.

3. **Collection of the Medicinal Product Data:**
   Medicinal product data sets corresponding to the 150 substances were obtained from the regulators.

4. **Pre-selection of Medicinal Product Data:**
   Three medicinal products per substance variant and dose form were selected for the end-to-end testing.

5. **Harmonisation of Medicinal Product Information:** Medicinal product information was reviewed using the Summary of Product Characteristics (SPC) provided by regulators. The information was globally harmonized and standardized for substance, dose form, and strength identification to ensure consistent PhPID construction.

   To assign one PhPID to products that are comparable or identical, even if described differently in SPCs across various jurisdictions, the concept of 'Harmonization' and specific business rules were developed and tested within the Global PhPID Service. This harmonization is both technology- and process-based, enabling the implementation of global IDMP. In cases where SPC information did not provide enough clarity, the "Five Region Check" approach was used.

6. **Five Region Check**
   This approach, implemented by UMC, aimed to mitigate regional variations during end-to-end testing. It involved analyzing substances and products across five key regions: Asia, Europe, Latin America, North America, and Oceania, to understand how specific substances or products are described globally. The steps included:
   1. **Selection:** Five products containing a specific substance variant and dose form were selected, one from each region.
   2. **Companion:** These products were examined in terms of strength, unit, and other relevant characteristics.
   3. **PhPID Harmonisation:** Harmonisation decisions were made based on identified variations.
   4. **PhPID Assignment:** A PhPID was assigned to each of the five products.

7. **Identifier Assignment:**
   Unique and harmonized pharmaceutical product identifiers (PhPIDs) were generated through:
   - Assigning a Global Substance Identifier (GSID) to each substance.
   - Mapping and validating dose forms and corresponding four attributes.
   - Applying business rules to harmonise strength expressions, units, and patterns.

8. **Construction of PhPIDs:** PhPIDs were generated using a MD5 hash algorithm.

9. **Stakeholder Engagement:** Regular interactions with regulators and GIDWG SMEs were maintained to address challenges and update processes and business rules.

10. **Outcome Review and Documentation:** Each test case was reviewed, documented, and categorized by pass/fail status, with supporting evidence captured in logs and other artifacts.

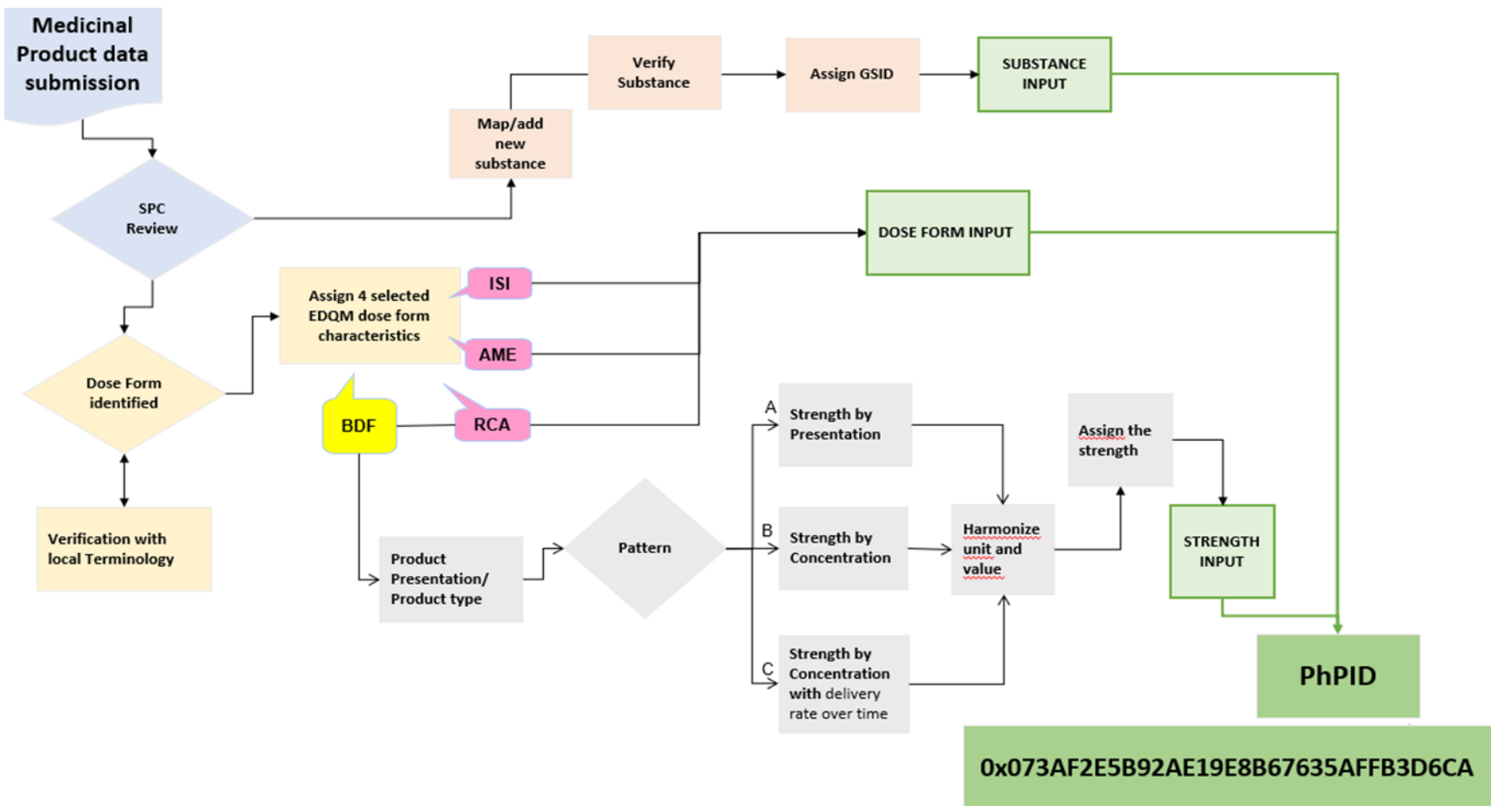


Figure 2: Steps for Generating PhPIDs during the End-to-End Testing

5. Results of End-to-End Testing

Summary of Results

The end-to-end testing of the Global PhPID Service Operating Model achieved a 90% success rate, demonstrating that the system's core functionality, business rules, and processes are robust. Approximately 2,645 of the 2,940 medicinal products tested were successfully assigned PhPIDs. While the high success rate underscores the system's effectiveness, the remaining 10% of unresolved cases highlight areas for further refinement.

Key Performance Metrics

1. **Test Coverage:**
   - 95% of the system's functionalities and processes were tested, including:
     - PhPID Requestor application
     - PhPID Validation System
     - PhPID Publisher
     - ISO IDMP Search in WHODrug
   - The ´Requesting PhPID " function requires additional development to meet full operational readiness.
2. **Global PhPID Service Readiness:**

   Readiness was assessed across three key three domains:
   - **Technical Readiness**:
     - **System Testing**: Functional, integration, user acceptance, and regression testing were completed.
     - **Backup and Recovery**: Backup and disaster recovery processes are in place.
     - **Infrastructure Setup**: Hardware, networking, and other infrastructure components are correctly configured.
     - **Security**: Security assessments, including vulnerability scans and penetration testing were completed.
     - **Configuration Management**: System configurations were documented, consistent, and version controlled.
     - **Integration Readiness**: Interfaces with third-party systems, APIs, and other integrations are still under development and require additional testing.
   - **Business Readiness**
     - **User Training**: User training is under development.
     - **User Documentation**: Comprehensive user manuals, quick reference guides, and other documentation are under development.
     - **SLA Agreements**: Service Level Agreements (SLAs) are under development.
     - **Stakeholder Approval**: Relevant stakeholders are being kept informed and updated.
     - **Communication Plan**: Communication plan is under development.
   - **Operational Readiness**
     - **Support Team Preparedness**: Both IDMP-trained pharmacist team and IT support team are trained and ready to handle issues that may arise post-go-live.
     - **Monitoring Tools**: Tools for monitoring system performance, error logs, and user activity are set up.

- **Help Desk/Customer Support**: A help desk and customer support are in place (IDMP support line).
- **Process Readiness**: Processes and business rules for medicinal product data processing and harmonization were successfully tested. However, four existing business rules were amended, nine new rules were formalized, and 17 current rules were refined.
- **Change Management**: A change management process is under development and must be tested.

Test Execution:
The end-to-end testing achieved a 90% success rate, with 2,645 out of 2,940 medicinal products successfully assigned PhPIDs under the current Global PhPID Service Operating Model (see Table 1). This impressive outcome highlights the robustness of the operating model and the stability of its business rules, even when tested with challenging substances and products under stress conditions.

However, approximately 10% of the medicinal products remain under evaluation, requiring further analysis to address unresolved issues. Details regarding these cases and the associated challenges are discussed in Section 6: Findings.

Table 1: Percentage of Medicinal Products Processed and Assigned Global PhPIDs

Regulator-Country	Medicinal Products Selected	Medicinal Products Processed* (raw data–(out-of-scope+not found))	Medicinal Products with Assigned PhPIDs	Success Rate
ANVISA / Brazil	**502**	**488** (502-(6+8))	**456**	93 %
Swissmedic/Switzerland	**540**	**525** (540-(1+14))	**467**	89 %
Health Canada/Canada	**240**	**230** (240-(9+1))	**198**	86 %
US FDA/USA	**806**	**752** (806-(9+45))	**678**	90 %
EMA/France, Greece, Croatia	**1099**	**949** (1099-(1+149))	**851**	90 %
All countries	**3187**	**2944**	**2650**	**90 %**

* Note: Some products were excluded because they contained substances or combinations outside the scope of the end-to-end testing, or they lacked a medicinal indication. Several products could not be processed due to the unavailability of SPCs or insufficient information for PhPID assignment (these are categorized as "Not found").

Defect Detection and Resolution: The testing resolved 88% of detected defects, issues, and challenges (260 out of 295 documented issues were resolved).

6. Findings

The findings from the end-to-end testing identified both successes and challenges in the Global PhPID Service Operating Model. This section outlines specific areas requiring refinement and provides insights into the harmonization and business rules for substances, dose forms, and strengths.

Harmonization Degree
The end-to-end testing evaluated the extent of medicinal product information harmonization across three key use cases: pharmacovigilance, drug shortages, and cross-border healthcare. As a general rule, the Summary of Product Characteristics (SPCs) for each product was individually examined, and global identifiers were assigned using the SPC as the primary source. For PhPID generation involving substances, dose forms, and strengths, minor differences in SPCs were harmonized to ensure consistency.

An important consideration for further evaluation is understanding how PhPIDs will be utilized in regulatory processes and systems. Key questions to address include: What is the optimal level of medicinal product information harmonization to deliver the most effective service? How should the balance be struck between providing detailed product representation and grouping similar products together for efficient use?

Recommendation: Identify specific areas for PhPID implementation to define the degree of medicinal product information harmonization required for PhPID generation. This could include developing guidelines for making informed assumptions.

Five Region Check:
This method proved valuable when validating additional products with the same substance variant and pharmaceutical form.

Example: In the case of amlodipine besilate, the Five Region Check involved verifying whether the strength of a product corresponded to the base amlodipine or the salt amlodipine besilate. If products across all five regions consistently expressed strength as corresponding to the base, it indicates a general practice, aiding in PhPID assignment for new products.

Recommendation: Establish a standard process for harmonization policy and evaluate the usage and risks associated with the Five Region Check.

6.1 Substance

6.1.1 Substance -specific Findings

6.1.1.1 Substance Definition and Global Substance Identification

Challenge: Approximately 150 substances, corresponding to approximately 350 substance variants, were included in the testing. GSIDs were assigned for substances and substance variants that were included in medicinal products sent in from the participating regulatory

authorities. Fewer than ten of the 150 substances were not assigned a GSID. The reason for not assigning a GSID were due to insufficient definitional information or conflicting information between two potential substances.

Recommendation: Establish a process for obtaining relevant information from stakeholders such as regulatory authorities or Marketing Authorization Holders (MAHs). This process is currently under investigation.

6.1.2 Harmonization Degree for Substance

6.1.2.1 Active Ingredient Harmonization

The PhPID generation process should utilize the active ingredient as stated in ISO 11616. The active ingredient can be either a base or salt variant; hydrates are excluded according to GIDWG business rules.

The next section addresses two issues:

a) Harmonizing the description of active ingredient variants (e.g., base vs. salt).

b) Differentiating substances classified as excipients or active ingredients (e.g., dextrose in nitroglycerin injections).

6.1.2.1.1 Harmonization of Salts Based on Substance

Challenge:

For liquid solutions, in rare cases when same substance is described differently among regulators, it was suggested that the active ingredient and its counter ion would exist in disassociated form in a solution. Therefore, two approaches (point 1 and 2 below) were tested for harmonization and a third alternative (point 3 below) could be considered:

1. **Harmonize by Active Ingredient and Counter Ion:** For instance, Methotrexate and Methotrexate sodium were treated as Methotrexate sodium if Methotrexate was the active ingredient with sodium listed as an excipient, or if Methotrexate sodium was the active ingredient.
2. **Harmonize by Active Moiety:** For Fluorouracil, both Fluorouracil and Fluorouracil sodium were harmonized to Fluorouracil.
3. **Follow Each SPC and Do Not Harmonize**: This approach was tested but showed the need for a more consistent harmonization method.

To achieve a consistent approach to harmonization, the initial attempt was to use Martindale as a reference, given its wealth of relevant information. When consulting Martindale, it provided clear guidance to harmonize Methotrexate sodium for liquid solutions. However, for Fluorouracil, Martindale did not offer definitive guidance. To ensure consistency, the decision was made to harmonize Fluorouracil to its active moiety.

This approach not only established uniformity but also streamlined the harmonization process, significantly reducing the need for manual intervention.

Recommendation: Evaluation of the PhPIDs generated based on the different approaches to ensure appropriate harmonization for the three use cases: pharmacovigilance, drug shortages, and cross-border healthcare. Adjust business rules as necessary based on evaluation results.

6.1.2.1.2 Harmonization of Salts Based on Medicinal Product

Challenge:

In some rare cases the active ingredient is described differently between regulators for the same products e.g., same Trade Name, dose form and Marketing Application Holder. Two approaches could be considered:

1. **Harmonize by Medicinal Product:** For instance, medicinal products containing Desmopressin vs. Desmopressin acetate, Dexamethasone vs. its salt variants were harmonized to the salt variant.
2. **Follow each SPC and do not harmonize.**

Martindale states that both active moiety and/or several substance variant(s) can be used for the investigated dose form for cases like Dexamethasone, and Rifampicin. During end-to-end the active ingredient of same products e.g., same Trade Name, dose form and Marketing Application Holder, were harmonized to the most specific substance variant when that was found in any SPC. However, some products are still being investigated.

Recommendation: Evaluation of the PhPIDs generated based on the harmonization to the most specific substance and decide if this is appropriate way of working or if the products should be validated by following the information in each SPC. Consider the three use cases (pharmacovigilance, drug shortages, and cross-border healthcare) and adjust business rules as needed.

6.1.2.1.3 Ingredient Classification: Active vs. Excipient

Challenge:

During the end-to-end testing, discrepancies were identified regarding whether a substance should be classified as an active ingredient or an excipient. The first case was if glucose used to administer glyceryl trinitrate (nitroglycerin) should be viewed as active or not. SPCs of six glyceryl trinitrate products were examined and compared, four of these products contained glucose and two products could be diluted with glucose solution. Of the four glucose-containing products, one SPC classified glucose as active, and the other three classified glucose as an excipient. The second case involves the active ingredient hetastarch combined with sodium chloride, which was described either as active or as an excipient. Eight SPCs were examined and five listed sodium chloride as an excipient and three listed it as active together with hetastarch. A clear business rule needs to be formulated to enable proper validation of these products.

Recommendation:
Develop business rules to classify substances consistently based on intended treatment purposes. Options include:
1. Following SPC classifications without harmonization - leading to similar products being separated at all PhPID levels.
2. Harmonizing based on treatment intent, disregarding other ingredients like glucose in PhPID generation.

6.2 Dose Form

6.2.1 Basic Dose Form (BDF)

6.2.1.1 Dispersible Tablet, Swallowed

The current business rules require the assignment of the Basic Dose Form (BDF) as follows:

- The BDF is verified in the Summary of Product Characteristics (SPC).
- The BDF used in PhPID construction always corresponds to the administrable dose form (AdmDF) as per the ISO 11239 standard.
- Only one BDF per AdmDF is assigned.

These rules mean that a dispersible tablet, which is dispersed in water before administration, would be assigned the BDF "Suspension." However, if a dispersible tablet can be either dispersed in water or swallowed whole, the primary use should be considered. In such cases, "swallowed whole" would take precedence, resulting in the BDF being assigned as "Tablet."

Table 2 below provides examples of dispersible tablets encountered during end-to-end testing, showing the administration method described in each SPC and the assigned dose form attributes.

Table 2: Dispersible Tablets

Medicinal Product	Country	"PDF" from SPC	Corresponding Administrable dose form	Administration method in SPC	Assigned BDF for PhPID
Amoxicillin Axapharm	Switzerland	Dispersible tablet	Suspension	*Swallowed whole or dispersed in water*	Tablet
Amoxicilline Almus	France	Dispersible tablet	Suspension	*Swallowed whole or dispersed in water*	Tablet
Amoxicilline Arrow	France	Dispersible film-coated tablet	Suspension	*Disperse in water*	Suspension
Metformine viatris	France	Dispersible tablet	Suspension	*Swallowed whole or dispersed in water*	Tablet
Nesh zinco	Brazil	Tablet for suspension	Suspension	*Swallowed whole, chewed or dispersed in water*	Tablet
Oracefal	France	Dispersible tablet	Suspension	*Disperse in water*	Suspension

Challenge: As displayed in the Table 2, products with the dose form term dispersible tablet/tablet for suspension may be assigned either BDF Tablet or Suspension based on the administration method in the SPC, which may affect heavily the effectiveness of medicinal information harmonization process and data quality for PhPID generation input, resulting in separating products with the same dose form term.

Recommendation:
Further evaluate whether the current business rule is sufficient. Alternatively, consider aligning BDF assignments solely with SPC dose form terms to avoid discrepancies. Consider conducting a comparison exercise on other business rules where assignment of the Dose Form ID (DFID) involves investigating various parts of the SPC to ensure correct DFID assignment.

6.2.1.2 Lack of Clarity in SPC on BDF

Challenge:
Regional terminologies for dose forms vary, making it difficult to align them with the EDQM dose form attributes used for PhPID generation. For example, terms such as 'Syrup,' 'Elixir,' 'Oral drops,' or 'Gel-cream' are used differently across jurisdictions. These terms may not align with the EDQM dose form attributes used for PhPID generation. According to current business rules, dose forms classified as Syrup should be assigned either the BDF term "Solution" or "Suspension" based on the information provided in the SPC. However, SPCs and local terminologies often lack sufficient detail, making it difficult to determine the appropriate term for PhPID. For instance, distinguishing whether a product labeled as 'Syrup' should be classified as a "Solution" or "Suspension" can be challenging.

Recommendation:
There could be two alternatives to consider for further evaluation:
- **Formalize Business Rules:** Establish clear business rules for managing similar cases, which should guide decisions when information gaps occur. Evaluate harmonizing such dose forms to less granular terminology, for example:
    - Use state of matter Liquid instead of the more specified BDF Solution or Suspension.
    - Assign BDF Solution regardless of if the precise term is solution/suspension/syrup/elixir.
- **Information Retrieval Process:** In cases where business rules do not cover information gaps, follow a dedicated process for information retrieval (e.g., liaising with MAHs).

6.2.2 Release Characteristics (RCA)

As per current business rule, based on EDQM definition modifications like Delayed, Prolonged, or Modified release, should be based on the formulation of the medicinal product compared to a conventional product with the same active ingredient(s). For instance, dexamethasone acetate is a long-acting variant where the acetate salt's properties, not the formulation, cause prolonged release. Therefore, a suspension for injection containing dexamethasone acetate would be assigned RCA "Conventional."

As shown in the Table 3 only one term is used for RCA.

Table 3: Combination of RCA for Capsules and Tablets		
		EDQM RCA used in PhPID
Conventional and Prolonged		Prolonged
Delayed and Prolonged		Prolonged
Conventional and Delayed	Combination of Immediate-Release and Delayed-Release with at least one ingredient exhibiting both release characteristics	Prolonged
	Combination of Immediate-Release and Delayed-Release where no ingredient exhibits both release characteristics	Delayed

Challenge: Current business rules, based on EDQM definitions, state that modifications such as Delayed, Prolonged, or Modified release should be determined by the formulation of the medicinal product compared to a conventional product with the same active ingredient(s). However, identifying whether a substance or its formulation is responsible for the release characteristics can be challenging, especially when this information is not clearly presented in the SPC.

For example, in the case of the product Vitamin D3 Streuli, an intramuscular injection containing colecalciferol, the RCA "Prolonged" was assigned based on the formulation’s description of its prolonged release into the bloodstream. This information was found in the pharmacokinetics section of the SPC, but it was not straightforward or easy to identify. Conversely, products with terms like "depot" or "prolonged" in their names may not always clarify whether the substance or formulation is responsible for the prolonged release, necessitating further examination.

Since information on release characteristics is not uniformly structured across SPCs globally, manual work to locate this information can be difficult and may require assumptions. Variations in dose form terminologies across countries further complicate the accurate assignment of release characteristics, particularly for products that combine multiple RCAs, such as those with both delayed and prolonged release properties.

During the end-to-end testing, it was noted that products like mesalazine have various formulations that affect their release, combining delayed and prolonged release properties.

Recommendation:

Propose further evaluation to address the following questions:

- Assess whether the current approach to handling prolonged release characteristics in medicinal products is viable.
- Determine the best method for generating non-specific base PhPIDs, such as RCA for oral mesalazine formulations.
- Evaluate the extent to which local terminology for dose forms should be considered when assigning RCA. Focusing solely on local terminology may lead to incorrect RCA assignments in some cases.
- Clarify how products should be handled when their release characteristics are not clearly described in the SPC.

6.3 Strength

6.3.1 Strength- Specific Findings

6.3.1.1 Mixtures

Challenge: Mixtures, defined as two or more substances that cannot be separated, pose challenges in assigning a correct average molecular weight, affecting the calculation of the Reference amount for salt variants of mixtures. A molecular weight can be assigned to each substance in the mixture, however, the ratio between the substances may vary leading to difficulties in assigning a correct average molecular weight for the mixture. Hence no specific molecular weight can be assigned for such Mixtures which will have an impact on the calculation of Reference amount for salt variants of mixtures. During the end-to-end testing the molecular weight was set to 1 while waiting for a technical solution.

Recommendation: Use molecular weight to calculate the Reference amount only, when necessary, i.e., for chemicals expressed in terms of amount and Reference amount. For substances that do not use Reference amount, consider introducing the possibility to indicate “Molecular weight N/A.”

6.3.2.1 Overfill

Challenge:

Current business rules specify excluding overfill when assigning strength for injections. However, the absence of explicit mentions of overfill in SPCs can lead to discrepancies in strength assignments across regions. This means that if the SPC indicates an overfill volume, the strength should be assigned based on the volume excluding the overfill. In some cases, overfill is assumed in the absence of explicit mention in the SPCs when comparing products across countries. Although the products may be described similarly, their strengths can vary. Table 4 below presents examples related to overfill.

Table 4: Overfill		
Overfill issues	**Description**	**Country**
Mylotarg (gemtuzumab ozogamicin)	SPCs were clear about overfill – Overfill excluded and PhPID strengths harmonized.	Brazil, Canada, Japan, Switzerland
Proleukin (aldesleukin)	SPCs unclear, products are described the same but do not mention overfill or similar – PhPID strengths were not harmonized.	Canada, France, Greece, Switzerland, USA
Cablivi (caplacizumab)	Strength is similar (10 mg and 11 mg) but nothing points towards overfill – PhPID strengths were not harmonized, which is why it has not been considered as overfill case.	Brazil, Canada, France, Switzerland, USA

Recommendation:
Further evaluate how to ensure accurate harmonization of PhPID strengths and determine when products should be classified separately.

6.3.2.2 Strength of Reference Substance Used to Calculate PhPID Strength

Challenge:
To standardize PhPID generation and ensure proper harmonization PhPID strength is calculated using the strength given in the SPC. However, when the active ingredient is a substance variant, the product strength may be given as the base rather than the active ingredient, leading to inconsistencies.

For example, calculating the PhPID strength from a given strength of 10 mg results in a PhPID strength of 13.87 mg for the following products:

- **Australian product "Ipca amlodipine 10 mg tablet"**
  - Amlodipine besilate 13.88 mg
  - Equivalent: amlodipine 10 mg
- **Irish product "Amlodipine 10 mg tablet"**
  - 10 mg tablet contains 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.

Recommendation:
Calculate the strength for the active ingredient and use it in PhPID generation. Ensure users can still search for the product by the given strength in the SPC.

6.3.2.3 Hydrates

Challenge:
Current business rules do not use GSID for hydrates in PhPID generation, but assigning SDID for hydrated substances is challenging. The strength listed in the SPC is used for PhPID generation, but inconsistencies in how strengths for hydrated substances are reported across SPCs create challenges. These inconsistencies occur both within and between different countries, leading to variations in how the strength is expressed—sometimes as the anhydrous form, other times as the hydrated form.

During the end-to-end testing, three categories were used:

1. Clear Hydrate Correspondence: When the SPC clearly indicates that the given strength corresponds to the hydrate form, the anhydrous strength is calculated based on the hydrate's strength, and this anhydrous strength is used for PhPID generation.

2. Given Strength Correspondence to Both Hydrated and Anhydrous Forms: In some cases, the given strength corresponds to both the hydrated and anhydrous forms of the substance. For instance, if the molecular weight difference between the hydrated and anhydrous forms is less than 5%, these products are considered similar or exchangeable. From a use-case perspective, they should be assigned the same PhPID. During end-to-end testing, the given strength was used as the PhPID strength in such cases, ensuring consistency across similar products.

3. Substance Definitions and differences in Molecular weight: Regulatory authorities globally may use different sources of substance information, some of which may not clearly indicate whether a substance is hydrated. For example, the USP (United States Pharmacopeia) might list desmopressin acetate without specifying that it includes the hydrate. This lack of clarity complicates the assignment of PhPIDs. During end-to-end testing, if the substance name did not include hydration information and the molecular weight difference between the hydrated and anhydrous forms was less than 5%, the given strength was used as the PhPID strength.

Despite these challenges, all medicinal products containing hydrated substances were successfully assigned a PhPID during the end-to-end testing.

Recommendation:
Given the significant variability in hydrate information across SPCs, there is a need for harmonization when assigning PhPIDs to comparable products. The approach tested during the end-to-end process—assigning PhPIDs based on the anhydrous strength or using the given strength where appropriate—worked well and should be considered for standardization. Further evaluation should be conducted to confirm this approach and determine if additional business rule adjustments are needed to address these scenarios consistently.

6.3.2.4 Unit Conversions

Challenge:

The absence of a globally approved unit conversion framework presents challenges in handling unit conversions (e.g., mg to IU). A proposal for using conversion tables in PhPID generation is being evaluated.

- A proposal for using conversion tables in PhPID construction was accepted by GIDWG and is being evaluated during end-to-end testing. To determine a global conversion factor, the following approach has been used:
  1. **Martindale Conversion:** When Martindale provides a clear conversion factor, it is used.
  2. **Official Conversion Tables:** Conversion factors from official tables in SPCs or authority documents are used. For example, see the conversion for Colistin in the table below.
  3. **Individual SPCs:** If the above sources do not provide a conversion factor, factors from individual SPCs in different countries are used, provided they are consistent. For example, see the conversion for Alteplase in the unit conversions table.

If discrepancies arise between SPCs, country references, and Martindale, an overall judgment is made, and the issue may be referred to GIDWG.

Choosing Between Units:

To minimize the number of unit conversions, a five-region check (described in the Methodology section) has been performed to identify the most used unit for PhPID generation. Table 5 below shows substances for which unit conversions have been performed during end-to-end testing. The Table 5 below illustrates substances for which unit conversions have been performed during end-to-end testing.

Table 5: Unit Conversions During End-to-End Testing

Substance	From unit	To PhPID unit	Conversion factor (Source)	Reason for decision
Alteplase	IU	mg	10 mg = 5.8 MIU (SPCs)	mg more common (5 region check)
Colecalciferol	TBD	TBD	1 IU = 0.025 mcg (Martindale)	Colecalciferol was evaluated before End-to-end and before the introduction of the Five region check. Therefore, it was assigned the unit mcg, however the Five region check show IU being more common. The suggestion is to change the unit from mcg to IU to avoid unnecessary unit conversions.
Colistin/ colistimethate sodium	Mg	IU	150 mg base = 360 mg salt = 4.5 MIU (EMA)	IU and mg equally common (5 region check). Substance is a mixture, meaning correct ration between salt and base in not possible to decide (see MW for colistin). Choosing IU ensures we get correct strength, since activity is not dependent on base/salt.
Desmopressin	IU	mcg	*Has not been needed during e2E*	mcg is more commonly used.
Lenograstim	IU	mcg	150 mcg = 19.2 MIU (Martindale)	IU and mg equally common (5 region check). The SPCs expressing strength in MIU also mention mcg, therefore mcg is used for PhPID.
Somatropin	IU/units	mg	3 units = 1 mg (Martindale)	mg more common (5 region check)
Tenecteplase	Units	mg	40 mg = 8000 units, 50 mg = 10000 units. (SPCs)	mg more common (5 region check).

Recommendation:

With the current approach, all substances, where unit harmonization was necessary, were successfully converted during end-to-end.

- Establish the use of conversion tables in business rules.
- Discuss whether unit conversions should be harmonized globally, particularly in cases where unit conversions do not match.

6.3.2.5 Specificity of Strength

Challenge:

The strength of a product may be expressed with varying levels of specificity in the SPC. During testing, the most specific strength was used, but inconsistencies arise when comparing rounded and more specific values. Additionally, products may be authorized with different levels of specificity, making it challenging to determine equivalence.

During end-to-end testing, the most specific strength identified has been used. For example, for the product Selincro (Nalmefene hydrochloride dihydrate), the strength listed as 18 mg in the name section and 18.06 mg in the strength section led to the use of the more specific strength (18.06 mg). When only a rounded strength is provided (e.g., 18 mg), it is harmonized to the more precise value of 18.06 mg.

Recommendation:

Evaluate whether PhPIDs should be updated to reflect the more specific strength or if the rounded strength should always be used for PhPID generation.

6.3.2.6 Harmonization of Pattern Framework for Liquid Preparations

The strength expression for PhPID generation—whether as concentration or presentation—is determined by three distinct patterns based on the dose form and use of the product. The Figure 3 simplifies the Pattern Framework to illustrate how the strength expression pattern is selected for PhPID generation. Note that many dose forms may fit multiple patterns depending on the product's use (e.g., total use parenteral liquids vs. partial use parenteral liquids).

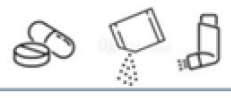
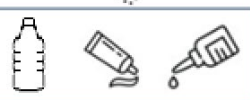
Pattern	Type of product	Strength (Presentation)	Strength (Concentration)
A		Mandatory	Empty
B		Empty	Mandatory
C		Empty	Mandatry- as a delivery rate over time

Figure 3: Strength Pattern Framework

During end-to-end testing, the pattern was generally assigned based on adult dosing without dosage reduction, even if dosing for children was also included in the SPC. For products or containers intended solely for children, the pattern was based on pediatric dosing. Each SPC was evaluated individually to determine the appropriate pattern based on intended use and dosage.

For parenteral liquid preparations (excluding metered-dose or powder forms):

- **Pattern A** is selected when only total use is mentioned (e.g., all normal adult doses correspond to a full vial/ampoule/syringe), typically expressed as mg.
- **Pattern B** is chosen for liquids in containers (e.g., vials, bags, ampoules) where individual dosing (e.g., dose/kg or dose/BSA) is specified as a normal adult dose, and/or at least one standard normal adult dose is a partial use, even if total use is also mentioned. This is usually expressed as mg/ml.

It has been observed that the dosing of products with the same concentration and presentation can be described differently in SPCs across regions, leading to varying pattern selections and, consequently, different PhPIDs under the current rules.

Recommendation: Propose further evaluation to address these discrepancies and clarify if pattern should be harmonized for all product with the same dose form and strength (e.g. applying harmonization business rules and/or Five Region Check) or assigned individually based on each SPC information.

6.4 PhPID Requesting Process

Challenge:
The PhPID request process, including data submission, has been time-consuming for all involved parties.

Opportunity: Develop a strategy for submitting and linking Local IDs (e.g., NDCs, PMS IDs) to PhPIDs to streamline validation and harmonization processes.

Recommendation: Evaluate strategies for handling Local IDs through the following methods:

- **Via API:**
  - Local IDs can be included in the request.
  - API requests must include an explanatory reference.
  - This approach reduces the risk of having duplicates.

- **Via PhPID Request Tool (Development in Fall 2024):**
  - The Excel template should include a dedicated column for local MPIDs.
  - The tool must be able to process this additional column.

6.5 Overarching PhPIDs

Opportunity: Regulators have expressed interest in having 'overarching' PhPIDs that group related substances, such as bases and their corresponding salts, to enhance aggregation and search functionalities in the Global PhPID Service.

Recommendation: Propose further evaluation to determine necessary developments and recommendations to ISO for amendments to ISO 11616.

7. End-to-End Use Case Results

The main goal of this report is to provide a comprehensive assessment of the end-to-end testing for evaluating the Global PhPID Service operating model (Service). This Service is designed to generate and maintain global PhPIDs for marketed medicinal products. The report examines the operating model's readiness for deployment, emphasizing software functionality, interoperability, processes, and business rules. The generation and maintenance of global PhPIDs are essential for three key global use cases: Pharmacovigilance, Drug Shortages, and Cross-border Healthcare.

7.1 Pharmacovigilance

One major benefit of implementing IDMP standards globally is improved surveillance and monitoring of substandard and falsified medicinal products. For instance, between October 2022 and December 2023, at least seven countries reported serious incidents involving over-the-counter paracetamol liquid products, leading to over 300 fatalities, primarily in children under five years old. Investigations revealed toxic levels of diethylene glycol and ethylene glycol as the cause, prompting six global medical alerts from the World Health Organization (WHO).

These alerts identified toxic levels of diethylene glycol and ethylene glycol, which can cause acute renal failure and fatalities. Although issued for specific batches in certain countries, the affected products may have marketing authorizations in other regions or could have been distributed informally.

Without a global PhPID, such alerts are fragmented across different product names and batch numbers, making it challenging to detect patterns and take swift regulatory action. Incorporating global PhPID identifiers in alerts would significantly enhance pharmacovigilance by enabling regulators to:

- Search pharmacovigilance databases for relevant individual case safety reports (ICSRs).
- Identify similar contamination patterns in other regions.
- Notify healthcare professionals, such as pediatricians and pharmacists, who can use identifiers in e-Prescribing and e-Dispensing systems to identify affected OTC products.

Additionally, integrating global PhPIDs into pharmacovigilance databases and e-prescribing, could significantly enhance the ability to search for affected products, such as filtering by specific dosage forms like syrups. Currently, products are often reported only by name or product line, making it difficult to identify related products associated with adverse events, such as acute kidney injury. The use of global PhPIDs could improve database searches, enabling the identification of similar products more efficiently. Since paracetamol is used in many OTC products, primarily tablets and capsules, signal detection at the substance level alone may miss issues with liquid forms. Table 6 shows examples across multiple dose forms from a database of 20,000 paracetamol medicinal products.

For example, since paracetamol is commonly used in many over the counter (OTC) products, primarily in tablet and capsule forms, signal detection at the substance level alone may miss issues specifically related to liquid forms. Using Global PhPID Level 3 (substance, dose strength, dose form attributes) would allow the identification of all medicinal products containing paracetamol in syrup form, filtering out other dose forms (See Table 7). According to current business rules, dose forms classified as "Syrup" or "Oral Drops" are assigned either the BDF term "Solution" or "Suspension," based on the information provided in the SPC.

Additionally, the implementation of PhPIDs on a global scale could streamline manual coding processes significantly. During end-to-end testing, the addition of PhPIDs to VigiBase demonstrated a reduction in manual re-coding time for drug information in ICSRs by 2,873 hours per year. This estimate was based on 3,160,656 ICSRs received by VigiBase in 2023, of which approximately 2% (63,212 ICSRs) required manual coding. The use of PhPIDs improved data granularity, enabled instant data retrieval for analysis, and enhanced overall data quality.

In summary, implementing global IDMP standards can improve alert communication, enable real-time identification of serious adverse events, and enhance public health safety across countries.

Table 6: Search Results of Paracetamol Products

19635 rows

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Product Name B3	Drug Code	Active Ingredients	ATC	Country of Sales	MAH	Pharmaceutical Form	Strength
LITTLE FEVERS	000200 01 954	Paracetamol	**N02BE,** Anilides *official*	Puerto Rico • United States of America	Medtech • Medtech labs • Prestige brands • Vetco	LIQUIDS • LIQUIDS, DROPS	80 mg • 80 mg/ml
INFANTS LITTLE REMEDIES FOR FEVERS	000200 01 A0R	Paracetamol	**N02BE,** Anilides *official*	Canada	Prestige brands	LIQUIDS	80 mg/ml
ACETAMINOPHEN NAEWOE	000200 01 A3J	Paracetamol	**N02BE,** Anilides *official*	Korea (the Republic of)	Nae woi	TABLETS	80 mg
BUBDEL	000200 01 BK3	Paracetamol	**N02BE,** Anilides *official*	Taiwan (Province of China)	Winston	TABLETS	80 mg
CAUSALON [PARACETAMOL]	000200 01 212	Paracetamol	**N02BE,** Anilides *official*	Argentina	Phoenix	LIQUIDS • LIQUIDS, DROPS • SUPPOSITORIES, ADULT • TABLETS • TABLETS, CHEWABLE	80 mg
CHILDREN'S CHEWABLE ACETAMINOPHEN	000200 01 982	Paracetamol	**N02BE,** Anilides *official*	Canada	Vita health products inc	TABLETS, CHEWABLE	80 mg
CHILDRENS MAPAP	000200 01 AXR	Paracetamol	**N02BE,** Anilides *official*	Puerto Rico • United States of America	Major Pharmaceuticals	TABLETS, CHEWABLE	80 mg
CORIVER INFANTIL	000200 01 BBI	Paracetamol	**N02BE,** Anilides *official*	Mexico	Maver	TABLETS	80 mg

Table 7: Search Results of Paracetamol Products

Medicinal Product Name	Drug Code	Active Ingredient(s)	ATC	WHODrug MPID	Authorization Country	MAH	Dose Form ⓘ	Strength (Reference Strength)
Children's tylenol	00020001246	Paracetamol	N02BE, Anilides	63709	Canada	McNeil Consumer Healthcare	Suspension	32 mg/mL
Cyfenol baby	00020001BD5	Paracetamol	N02BE, Anilides	4989075	Brazil	Cifarma	Suspension	100 mg/mL
Tyflen	00020001567	Paracetamol	N02BE, Anilides	5155395	Brazil	Brasterapica	Suspension	100 mg/mL
Tyflen	00020001567	Paracetamol	N02BE, Anilides	5155398	Brazil	Brasterapica	Suspension	32 mg/mL
Tylemax crianca	00020001BGB	Paracetamol	N02BE, Anilides	5155429	Brazil	Natulab	Suspension	32 mg/mL

Medicinal Product Name	Drug Code	Active Ingredient(s)	ATC	WHODrug MPID	Authorization Country	MAH	Dose Form ⓘ	Strength (Reference Strength)
Children's tylenol	00020001246	Paracetamol	N02BE, Anilides	5504746	Canada	McNeil Consumer Healthcare	Solution	160 mg
Cimegripe 77c	00020001A1E	Paracetamol	N02BE, Anilides	5492080	Brazil	Cimed	Solution	500 mg
Dafalgan	00020001057	Paracetamol	N02BE, Anilides	60409	Switzerland	Upsamedica SA	Solution	500 mg
Dafalgan	00020001057	Paracetamol	N02BE, Anilides	60413	Switzerland	Upsamedica SA	Solution	1 g
Dorsanol	00020001580	Paracetamol	N02BE, Anilides	3004209	Brazil	Multilab	Solution	500 mg
Emsgrip	00020001564	Paracetamol	N02BE, Anilides	5370809	Brazil	Ems sigma pharma	Solution	500 mg
Fervex	00020001BR1	Paracetamol	N02BE, Anilides	5371458	Brazil	Kley hertz	Solution	500 mg
Paracet	00020001023	Paracetamol	N02BE, Anilides	5404202	Norway	Karo pharma	Solution	24 mg/mL
Paracet	00020001023	Paracetamol	N02BE, Anilides	5404195	Norway	Karo pharma	Solution	500 mg
Paracetamol	00020001001	Paracetamol	N02BE, Anilides	5373883	Brazil	Ems industria farmaceutica	Solution	500 mg
Paracetamol norfri	00020001AWU	Paracetamol	N02BE, Anilides	4412213	Norway	Evolan Pharma AB	Solution	500 mg
Paracetamol norfri	00020001AWU	Paracetamol	N02BE, Anilides	4330342	Norway	Evolan Pharma AB	Solution	24 mg/mL
Pinex	00020001021	Paracetamol	N02BE, Anilides	5404898	Norway	Actavis	Solution	500 mg
Pinex	00020001021	Paracetamol	N02BE, Anilides	5404923	Norway	Actavis	Solution	24 mg/mL
Resfenol thermus	00020001A1U	Paracetamol	N02BE, Anilides	2886397	Brazil	Hertz	Solution	500 mg

7.2 Drug Shortage

In 2023, a drug shortage involving cisplatin in the United States highlighted the importance of global product identification. The shortage stemmed from was a quality-related manufacturing issue at a key production site, which disrupted supply chains.

Initially, efforts to source cisplatin focused on domestic manufacturers, but these attempts failed to meet demand. Regulatory authorities turned to international markets to locate alternative sources. However, this presented numerous challenges, including variations in strength and potency, differences in packaging, and the need to verify product quality and supply chain reliability.

Other approved Marketing Authorization Holders were unable to meet the increased demand. In such situations, the US marketing authorization holder must notify the FDA that it cannot fulfill patient demand for cisplatin. The initial step is to contact other approved or pending US application holders to see if they can increase production.

If the shortage persists, the next step is to reach out to international regulatory authorities to find potential non-US sources of cisplatin. Challenges in sourcing from other countries include:

1. Availability of sufficient quantities.
2. Variations in strength and potency.
3. Differences in packaging and labeling.
4. Absence of local or regional distributors.
5. Importation delays.
6. Verification of product quality and compliance with regulatory standards.
7. Supply chain reliability.
8. Effective communication and transparency among manufacturers, regulators, healthcare providers, and patients.
9. Prioritization of medical needs to ensure patient safety.

Prompt regulatory action is essential to protect patients, but identifying a suitable foreign substitute can be challenging and time-consuming. Initially, the search for cisplatin was limited to approved FDA manufacturing sites in two regions. Evaluating global cisplatin facilities was difficult due to a lack of international interoperability and standardized global identifiers.

In May 2023, four months into the shortage, the FDA announced the temporary importation of non-US-labeled cisplatin injection. To address the shortage quickly, the imported product was not relabeled or repackaged, as communicated in a "Dear Healthcare Professional" letter to stakeholders.

Table 8 presents a comprehensive listing of cisplatin products by key attributes, including MAH, dose form, strength, and global PhPID. This table illustrates how standardized identifiers, like the global PhPID can streamline the identification process during a shortage.

Table 8: Search Results of Cisplatin Products and Associated Global PhPID

Medicinal Product Name	Drug Code	Active Ingredient(s)	ATC	WHODrug MPID	Authorization Country	MAH	Dose Form ⓘ	Strength (Reference Strength)	PhPID	PhPID Level
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5533172	United States of America	Teva Parenteral Medicines	Solution	1 mg/mL	201F66CFC7F355D71215441005A45BE2	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5514896	China	Dezhou Deyao Pharmaceutical Co., Ltd	Solution	20 mg	7CBB36B430E420437E6A6C611A30234E	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	4012296	United States of America	Accord Healthcare	Solution	1 mg/mL	201F66CFC7F355D71215441005A45BE2	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5514890	China	Shandong luoxin ph	Solution	10 mg	45C5F86575708AAAC4D6EFAEA854DCEC	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	3020616	Canada	Teva Canada Ltd	Solution	1 mg/mL	201F66CFC7F355D71215441005A45BE2	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5646835	China	Qilu Pharmaceutical Company	Solution	1 mg/mL	201F66CFC7F355D71215441005A45BE2	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5113842	China	Qilu Pharmaceutical Company	Solution	20 mg	7CBB36B430E420437E6A6C611A30234E	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5508042	United States of America	Fresenius kabi usa	Solution	1 mg/mL	201F66CFC7F355D71215441005A45BE2	4
Cisplatin	00412101001	Cisplatin	L01XA, Platinum compounds	5533184	United States of America	Mylan	Solution	1 mg/mL	201F66CFC7F355D71215441005A45BE2	4

A global PhPID could significantly improve the management of drug shortages. By enabling the quick identification and access to similar products, regardless of their country or region of approval, global PhPIDs facilitate faster and more efficient responses to patient needs.

Implementing global IDMP standards, particularly the global PhPID, has the potential to reduce the time required to identify alternative or substitute medicinal products from week or months to mere days. This capability would allow drug shortage teams to allocate their time and resources more effectively.

7.3 Cross-Border Healthcare

Hypothetical Use Case

Ahmed, a patient from Saudi Arabia, travels to Brazil for a vacation but realizes he has forgotten his essential medication at home. Ahmed has a history of cardiovascular events, making it critical for him to take his atorvastatin daily to maintain therapeutic cholesterol levels and prevent further cardiovascular risks. Missing even a few doses could result in fluctuating cholesterol levels and diminished protection against potential cardiovascular events.

Leveraging a healthcare mobile app, Ahmed accesses an electronic prescription for his medication. The app allows him to generate a partly Portuguese-translated version of the prescription, which he presents to a pharmacist in Brazil. However, in Brazil, only a limited number of pharmacies are equipped to dispense foreign prescriptions. Fortunately, Ahmed finds one in the city he is visiting.

The prescription included headers in English, while the remainder was in Arabic. the prescription provided all the required information, including patient and prescriber details, the brand name of the drug, and the dosage of 20 mg in tablet form. However, the Arabic brand name cannot be entered into the pharmacy's software system, creating concerns about possible misinterpretation or dispensing errors.

Fortunately, the prescription includes a global PhPID level 4 identifier, allowing the pharmacist to search for medicinal products approved in Brazil that share the same PhPID (See Figure 4). The global PhPID eliminates the language barrier, allowing the pharmacist to quickly locate the equivalent atorvastatin product in Brazil. The ensures Ahmed can continue his therapy uninterrupted.

Figure 4

This scenario highlights the importance of global PhPIDs in overcoming linguistic and regulatory barriers, particularly when accessing important healthcare services in foreign countries. By providing a universal identifier, PhPIDs facilitate accurate product matching across regions, ensuring therapy compliance and patient safety. Table 9 presents the search results, highlighting product equivalence for atorvastatin across seven countries, as identified by their global PhPIDs.

Table 9: Search Results of Atorvastatin Products and Associated Global PhPID

Medicinal Product Name	Drug Code	Active Ingredient(s)	ATC	WHODrug MPID	Authorization Country	MAH	Dose Form ⓘ	Strength (Reference Strength)	PhPID	PhPID Level
Ateroma	01326102A11	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5160204	Brazil	Supera	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorva	01326102050	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	2126339	Saudi Arabia	Jazeera pharmaceutical industries	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorvastatin aristo	01326102816	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5116694	Norway	Aristo Pharma	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorvastatin calcium	01326102001	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	4323452	United States of America	Zydus Pharmaceuticals	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorvastatin Hexal	01326102465	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5204648	Norway	Hexal AS	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorvastatin pensa	01326102A1H	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5243697	Norway	Pensa Pharma	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorvastatin xiromed	01326102852	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	4188988	Norway	Medical valley invest	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Atorvastatine alter	01326102A37	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5613006	France	Alter	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Calipra	01326106017	Atorvastatin calcium trihydrate	C10AA, HMG CoA reductase inhibitors	3076262	Croatia	Alkaloid	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Lipitor	01326102016	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5404037	Norway	Orifarm	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Lipitor	01326102016	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	5413494	United States of America	Pfizer	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4
Rotacor	01326102114	Atorvastatin calcium	C10AA, HMG CoA reductase inhibitors	2868328	Greece	Sandoz	Tablet	20.68 mg (20 mg)	B07AB59004B325DFFBAD54CE05E74FE7	4

Implementing global PhPIDs within cross-border healthcare can enhance patient safety, ensuring that patients can continue their prescribed treatments without interruption when traveling or temporarily relocating, thereby reducing the risk of complications from missed doses. This use case illustrates the value of PhPIDs in creating a seamless global healthcare experience, regardless of linguistic or geographic barriers.

8. Discussion

The test results provide valuable insights into the performance and robustness of the Global PhPID Service Operating Model, particularly in assigning Pharmaceutical Product Identifiers (PhPIDs) to medicinal products and evaluating the readiness of the associated Harmonization Business Rules.

Test Execution Overview

The tests achieved a 90% success rate, successfully executing most test cases and assigning PhPIDs to the majority of medicinal products. This indicates that the operating model is functioning effectively, with well-designed and robust processes and business rules. The results demonstrate that the key functionalities and workflows of the operating model are both robust and well-validated. However, the remaining 10% of test cases that did not pass require further analysis to understand the underlying issues.

PhPID Assignment Performance

PhPIDs were successfully assigned to 90% of the medicinal products tested, with 2,645 out of 2,940 products correctly identified. This high success rate underscores the effectiveness of the operating model, even when applied to complex substances and challenging products. The consistency of success rates across participating countries (ranging from 86% to 93%) is a strong indicator that the model is ready for broader global implementation. The consistency of these success rates across regions highlights the stability of the processes and business rules, as well as their ability to address regional variations in substance, dose form, and strength descriptions.

Areas of Concern: 10% Under Evaluation

While the high success rate demonstrates the robustness of the Global PhPID Service Operating Model, approximately 10% of the medicinal products (295 out of 2,940) remain under evaluation. These unresolved cases point to specific areas where the operating model requires further refinement.

The underlying reasons for these unresolved cases need to be carefully analyzed. They may stem from:

- Complexities inherent to the substances and products themselves, such as mixtures or unique formulations.
- Limitations in the current business rules, such as inconsistencies in handling strength calculations or excipient classifications.
- Gaps in the operating model, including potential inefficiencies in harmonization processes or insufficient data quality standards.

Implications and Next Steps

While a 90% success rate is impressive, the unresolved 10% could have significant implications, especially if these products represent critical or widely used cases (e.g., in the harmonization of strength definitions). Resolving the identified issues is critical to achieving a fully reliable and globally applicable operating model.

The findings from the unresolved cases should guide ongoing improvements to the operating model. Refining business rules, enhancing data quality, and developing advanced algorithms to address complex cases will be critical for achieving greater reliability and effectiveness.

Additional testing may be required, particularly focused on the Change Management model and the 10% of products that have not yet been successfully processed. This could involve targeted tests on specific scenarios or substances that have proven difficult to handle.

9. Recommendations and Conclusions

9.1 Recommendations

The results of the end-to-end testing highlight both the strengths and the areas for improvement in the Global PhPID Service Operating Model. The following recommendations are proposed to guide the refinement and future development:

1. **Refine and Standardize Business Rules:**
   Inconsistent descriptions of substances like methotrexate and its salt forms revealed jurisdictional discrepancies. For instance, "Methotrexate sodium" was classified as an active ingredient in some regions, while others listed it as simply "Methotrexate." Such differences require standardization in business rules to ensure consistent descriptions and accurate classification of active ingredients versus their corresponding salts. Additionally, challenges with classifying glucose in glyceryl trinitrate products underscore the need for clearer differentiation between excipients and active ingredients.

2. **Strengthen Quality of Input Data:**
   Ambiguities in Summary of Product Characteristics (SPCs) complicated the assignment of Basic Dose Forms (BDF). For example, dispersible tablets were sometimes described with administration instructions indicating both swallowing whole and dispersing in water. This ambiguity led to confusion in categorizing the dose form as either "Tablet" or "Suspension." Developing standardized SPC guidelines would help stakeholders resolve these ambiguities, resulting in more precise and reliable data inputs for PhPID generation.

3. **Evaluate and Expand the Change Management Model:**
   Refining business rules during testing addressed evolving data requirements, such as overfill and unit conversion inconsistencies. For example, discrepancies arose in strength calculations for products like Mylotarg (gemtuzumab ozogamicin) and Proleukin (aldesleukin) due to inconsistent mentions of overfill in SPCs. Establishing a proactive change management model—addressing business rules, evolving data requirements, process flows, and stakeholder engagement—is critical to adapt effectively to such challenges in the future.

4. **Expand Use Case Testing:**
   As the PhPID service rolls out, additional testing focused for challenging substances and emerging scenarios is essential. Simulating real-world events such as drug shortages, cross-border prescriptions, and pharmacovigilance alerts will provide valuable insights into system functionality under varying conditions and inform refinements to better support the use cases.

5. **Introduce Overarching PhPIDs and Improve Data Aggregation:**
   Creating overarching PhPIDs to group related substances (e.g., bases and salts) would enhance aggregation and search capabilities within the Global PhPID Service. A thorough evaluation should be conducted to explore the necessary developments and to recommend potential updates to ISO IDMP standards. This approach aims to simplify data organization and improve the system's ability to present comprehensive information.

9.2 Conclusions

The Global PhPID Service Operating Model has demonstrated its robustness, achieving a 90% success rate in generating global PhPIDs for marketed medicinal products across five regulatory regions. This success underscores the model's core functionality and the effectiveness of its business rules.

The unresolved 10% of cases expose areas requiring targeted refinements. In the next phase, emphasis should be placed on:

- Refining business rules.
- Improving data input quality.
- Enhancing collaboration with stakeholders.
- Expanding training and capacity-building efforts.

These efforts will transition the Service from a successful testing phase to a fully implemented, reliable solution capable of supporting global pharmacovigilance, addressing drug shortages, and enhancing cross-border healthcare.

By addressing these challenges and seizing opportunities for improvement, the Global PhPID Service will meet its immediate objectives while laying the groundwork for future advancements and global harmonization. This comprehensive approach will ultimately enhance public health outcomes and create more efficient, unified regulatory processes worldwide.