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Review

Harmonization of individual case safety reports transmission requirements among PAHO reference authorities: a review of their current regulation

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***Abstract*:** To perform optimal monitoring of the safety profile in the postmarketing phase, Marketing Authorization Holders and National Regulatory Authorities (NRAs) must evaluate the adverse drug reactions (ADRs) that occurred and characterize their nature, frequency, and severity. Management is possible through Individual Case Safety Reports (ICSRs), which are the reports of organized and processed data. Globally, the International Council for Harmonisation (ICH) E2B guideline suggests harmonized activities for the ICSR electronic content and transmission. In America, the Pan American Health Organization (PAHO) is the agency responsible to implement cooperation among its members, which are recognized as National Regulatory Authorities of Reference (NRARs) such as Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and the United States. PAHO published the 'Good Pharmacovigilance Practices for the Americas' suggesting improvement and harmonization in the region. After reviewing the regulatory framework, it is assumed that all NRARs have a regulated ICSR transmission system (i.e. a systematic vigilance system for collecting, analyzing, and disseminating information from ADRs). However, significant differences exist, such as the requirement for social media vigilance, expedited and non-expedited ICSRs, coding, severity, and transmission. The volume of ICSRs has significantly increased, due to using electronic standards managed by the NRAs, which facilitates early identification of new ADRs, allowing the implementation of novel minimization activities, contributing to the continuous assessment of the benefit-risk balance of medicines. Nevertheless, there is still area for improvement, especially in Latin America.

Plain language summary

Transmission of spontaneous adverse drug reactions by industry in countries designated as a reference by the Pan American Health Organization (PAHO): comparison on regulatory requirements

This review aims to describe regulatory criteria and compare harmonization across regions that marketing authorization holders must fulfill when transmitting spontaneous adverse drug reactions to the authorities for postmarketing surveillance. It centers on the regulatory requirements of authorities designated as a reference by the PAHO. Consequently, it is important to review the regulatory framework, to evaluate the requirements for transmission and have the context of the current harmonization among these agencies in America. This review contains the minimum criteria for transmission and harmonized

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guidelines according to the International Council for Harmonisation (ICH) and PAHO. However, identifying the differences is only the first step, future research in harmonization must continue to advance the understanding and establish guidelines that allow a better evaluation of the safety profile of medical products.

Keywords: adverse drug reaction, harmonization, Individual Case Safety Report, National Regulatory Authority, National Regulatory Authorities of Reference

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Introduction

In 1961, the thalidomide catastrophe initiated the need for safety surveillance of medicinal products. As a result, in 1968 Australia, Canada, Germany, Ireland, Netherlands, New Zealand, Sweden, the United Kingdom, and the United States created the World Health Organization (WHO) Programme for International Drug Monitoring (PIDM), intending to ensure the timely identification of safety problems for medicines.[1–3] Furthermore, within the National Regulatory Authorities (NRAs) involved in postmarketing surveillance, evaluation enabled the acquisition of new knowledge of medicines' benefit–risk and risk communication.[4] This way, we can establish that an important part of pharmacovigilance (PV) is the communication by health professionals, caregivers, and patients reporting any suspected adverse drug reaction (ADR).[5]

The WHO defines PV as 'the science and activities relating to the detection, assessment, understanding, and prevention of the adverse effects or any other possible drug-related problems'.[6] Therefore, PV activities such as, evaluating spontaneous reports on suspected ADRs (currently the primary source of information) are necessary to take crucial decisions on pharmacotherapy at different levels: personal, national, regional, and international.[5] The WHO describes an ADR as: 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological functions'.[7] Hence, in order to ensure the safety of medicinal products in the postmarketing phase, Marketing Authorization Holders (MAHs) and NRAs must evaluate the suspected ADRs occurred and characterize its nature, frequency, and severity.[7]

Establishing a PV system by NRAs is expected to allow a thorough examination of data collection for detecting safety signals and use this information to implement regulatory actions.[8] Globally, ADR management is maintained in the WHO database known as 'VigiBase®', coordinated by Uppsala Monitoring Centre (UMC), where PIDM members (153 full members and 22 associate members)[1] transmit ADRs.[9] Therefore, considering the aid of efficiency of transmission reports shared with VigiBase, and the necessity to standardize transmission as part of data aggregation to support the surveillance, a strategy was initiated. Hence, it seeks to harmonize the transmission of ADR reports; from this perspective, it occurred under the International Council for Harmonisation (ICH) guideline E2B. Management is also possible through Individual Case Safety Reports (ICSRs), which are the report of organized and processed data by an organization with the information provided by a reporter at a certain point to describe an ADR.[7] Summarized, the ICSR under E2B format includes relevant data elements divided into two main sections: the 'Administrative and Identification Information' and the 'Information of the Case'; the second one includes the patient characteristics, reaction/event, results of tests and procedures relevant to the investigation of the patient, drug information, and narrative case summary.[10] Furthermore, the electronic submission of ICSRs under the E2B format facilitates transmission making it readily available for

Table 1. Overview of PAHO's system for evaluation of the NRARs.[13]

(A) Critical indicators to be assessed

National regulatory system	Marketing authorization	Manufacturing	Market surveillance
Pharmacovigilance	Control of clinical trials	Regulatory inspections and audit activities	Quality control national laboratory

(B) Results of the assessment

- ✓ *Level 4:* National Regulatory Authority competent and efficient in the performance of health regulatory functions recommended by PAHO/WHO. Denominated as NRAR.
- ✓ *Level 3:* National Regulatory Authority competent and efficient, which shall improve performance.
- ✓ *Level 2:* Organizations with the mandate of the National Regulatory Authority that fulfill certain health regulation functions recommended.
- ✓ *Level 1:* Office of health institutions that fulfill certain health regulation functions.

(C) Member states of the PAHO[12]

- Antigua and Barbuda	- Dominican Republic	- Peru
- Argentina*	- Ecuador	- Saint Lucia
- Bahamas	- El Salvador	- St. Vincent and the Grenadines
- Barbados	- Grenada	- St. Kitts and Nevis
- Belize	- Guatemala	- Suriname
- Bolivia	- Guyana	- Trinidad y Tobago
- Brazil*	- Haiti	- United States*
- Canada*	- Honduras	- Uruguay
- Chile*	- Jamaica	- Venezuela
- Colombia*	- Mexico*	
- Costa Rica	- Nicaragua	
- Cuba*	- Panama	
- Dominica	- Paraguay	

(D) Regional Reference Authorities of Reference for medicines

Argentina (ANMAT)	Brazil (ANVISA)	Canada (Health Canada)	Chile (ISP)
Colombia (INVIMA)	Cuba (CECMED)	Mexico (COFEPRIS)	United States (FDA)

According to PAHO's resolution CD50.90 for the regulatory systems strengthening, considers pharmacovigilance activities as one of the critical indicators necessary to obtain recognition as a NRAR (level 4 of the assessment).[13]
*National Regulatory Authority of Reference.
ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica; ANVISA, Agencia Nacional de Vigilancia Sanitaria; CECMED, Centro para el Control Estatal de la Calidad de los Medicamentos; COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios; FDA, Food and Drug Administration; INVIMA, Instituto Nacional de Vigilancia de Medicamentos y Alimentos; ISP, Instituto de Salud Pública; NRAR, National Regulatory Authority of Reference; PAHO, Pan American Health Organization; WHO, World Health Organization.

further processing and assessment; in that case, not only NRAs must share ICSRs, but also MAHs and potentially other bodies (e.g. clinical investigators, *via* the sponsor of a clinical trial, to ethics committees) do.[11]

In America, the Pan American Health Organization (PAHO) is responsible for engaging in technical cooperation with its members (Table 1) to strengthen health systems.[12] Moreover, to recognize agencies as National Regulatory Authorities of Reference (NRARs), PAHO evaluates according to different indicators. Evaluation results reflect the fulfillment within four levels; those with a high level are designated to level 4 (Table 1), being PV, a critical indicator evaluated to get designated agencies (NRARs), whose reach includes a high level of regional development; nowadays, Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and the United States

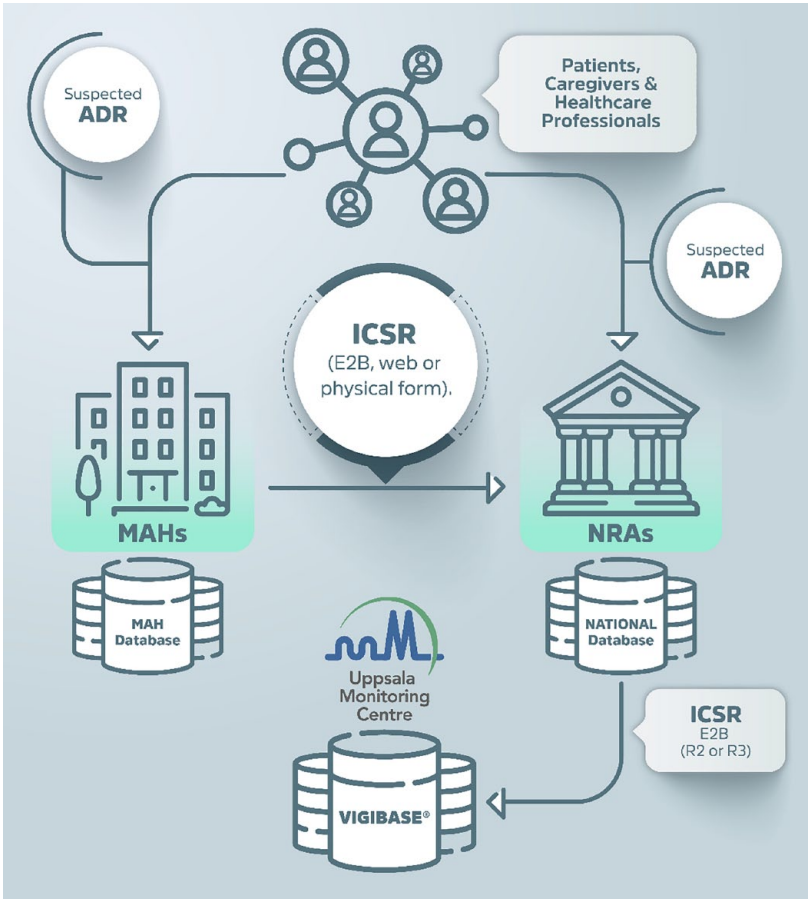

Figure 1. Postmarketing spontaneous ICSR transmission network.
Postmarketing spontaneous ICSR transmission network. Spontaneous notifications can be communicated to the MAHs or the NRAs; if the notification is made to the MAHs, they are responsible for transmitting the report to the NRAs with the minimum information and the analysis of the information. Once ICSR has been received, NRAs belonging to PIDM must send the compiled regularly to UMC to enter the VigiBase database and its analysis globally. As the above, communication was harmonized using electronic files quickly and with approved information considering the different agents that must be transmitted, such as the case of MAHs, and NRAs.
ADR, adverse drug reaction; ICSR, Individual Case Safety Report; MAHs, Marketing Authorization Holders; NRAs, National Regulatory Authorities; PIDM, Programme for International Drug Monitoring; UMC, Uppsala Monitoring Centre.

are members (Table 1).[13] However, though NRARs from the United States and Canada were founding members of PIDM, resulting in PV systems with more experience, Latin American NRAs, whose inscription began from 1990 to earlier 2000s, are still under development.[14] Therefore, improvement and harmonization in the region were created by PAHO and the PV group of the Pan American Network for Drug Regulatory Harmonization publishing in 2011 the 'Good Pharmacovigilance Practices for the Americas', with recommendations to get harmonized activities focused to the NRAs from Latin America.[5]

One of the objectives of harmonized regulation is to improve standardization in the processing of ICSRs.[11] Therefore, the PAHO considers the development and adherence to international guidelines for harmonization to strengthen, promote, and adopt good pharmacovigilance practices (GPVPs).[5] However, different requirements in the ICSR results in a multiplicity of contents across regions, increase the workload for reporters and challenges the reconciliation, which affects the reception, follow-up, and transmission.[11] For this reason, this review aims to compare the NRARs requirements and harmonization for ICSR transmission that could affect the drug safety assessment.

Methodology

A search was conducted on the official website and official gazettes of the NRARs as the current postauthorization regulation as of November 2022 [Argentina – ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica),[15] Brazil – ANVISA (Agencia Nacional de Vigilancia Sanitaria),[16,17] Canada – Health Canada,[18,19] Chile – ISP (Instituto de Salud Pública),[20,21] Colombia – INVIMA (Instituto Nacional de Vigilancia de Medicamentos y Alimentos),[22] Cuba – CECMED (Centro para el Control Estatal de la Calidad de los Medicamentos),[23,24] Mexico – COFEPRIS (Comisión Federal para la Protección contra Riesgos Sanitarios),[25,26] and the United States – FDA[27,28]]; as well as, PAHO[29] and ICH[30] regarding ICSR requisites were reviewed.

Background of ICSR transmission

Patients, health professionals, and caregivers can conduct communication of ADRs to NRAs or MAHs; the latter are legally responsible for their products' safety. When the MAHs receive an ICSR, they are responsible for transmitting it to the NRAs in complying with deadlines stipulated in each legislation.[5] The information is transmitted through physical or electronic forms.[1] Once the information is received, the NRAs send the

Table 2. Worldwide pharmacovigilance panorama for PAHO's National Regulatory Authorities of Reference.

Country	National Regulatory Agency[13]	PIDM year membership[1]	ICH member or observer[31]	ICH year membership[31]
Argentina	ANMAT	1994	Observer	2019
Brazil	ANVISA	2001	Member	2016
Canada	Health Canada	1968	Member	2015
Chile	ISP	1996	Neither member nor observer	Not applicable
Colombia	INVIMA	2004	Observer	2017
Cuba	CECMED	1994	Observer	2016
Mexico	COFEPRIS	1999	Member	2021
United States	FDA	1968	Member	1990

ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica; ANVISA, Agencia Nacional de Vigilancia Sanitaria; CECMED, Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos; COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios; FDA, US Food and Drug Administration; ICH, International Council for Harmonisation; INVIMA, Instituto Nacional de Vigilancia de Medicamentos y Alimentos; ISP, Instituto de Salud Pública; PAHO, Pan American Health Organization; PIDM, Programme for International Drug Monitoring.

compilation of ICSR to the UMC, thus being collected in the VigiBase database (Figure 1).[2]

To harmonize regulatory and ICSR requirements, NRARs participate in the PIMD[1]; even some of these are members of ICH (Table 2); the last one, also suggests ICSR transmission per the E2B guide (first published in 2001).[31] After 2005, version (R2) of this guide incorporated the XML (eXchange Markup Language) files to facilitate transmission.[11,32,33]

Since its implementation in 2006, various developments in electronic reporting requirements and GPVPs have stimulated the updating of the ICH E2B (R3) guide, which considers a collaboration between the ICH and Standards Development Organizations (e.g. the International Organization for Standardization) with new requirements for regulatory compliance of MAHs and other members of the PV system, such as the implementation of different terminologies and vocabularies in the ICSR message, for example, the inclusion of Drug Identification as the identification of product medicines (IDPM).[34]

Benefits of harmonization of ICSRs include the content in a homologated form and the ability for two or more systems to exchange and use such information, avoiding duplication in coding, and improving processing.[35] Getting the information in a global database facilitates tracking and allows its assessment by the NRAs.[5] As a result, this allows the identification of new adverse reactions and their timely prevention potentially if risks can be minimized through the analysis of the information obtained, and the implementation of minimization activities by the MAHs, with helpful information that supports decisions in the pharmacological treatment of patients.[36]

Comparison of the ICSR requirements among NRARs

Table 3 describes a comparison of ICSR requisites applicable to MAHs regarding transmis-

Table 3. Comparison of postmarketing requirements of ICSRs among the PAHO's National Regulatory Authorities of Reference.

ICSR postmarketing requirements	ANMAT (Argentina)	ANVISA (Brazil)	Health Canada (Canada)	ISP (Chile)	INVIMA (Colombia)	CECMED (Cuba)	COFEPRIS (Mexico)	FDA (United States)
Postmarketing unsolicited reports	Spontaneous reports[37]	Spontaneous reports[38]	Spontaneous reports, and reports *via* the Internet[38]	Spontaneous report[39]	Spontaneous reports[40]	Spontaneous reports *Note*: Unconditional spontaneous ADRs are not transmitted.[41]	Spontaneous report[42]	Spontaneous reports, and reports *via* the Internet[28]
Seriousness	Serious: It causes death or life-threatening, requires, or prolongs hospitalization, produces a congenital anomaly, or leaves a permanent sequela.[37]	Serious: Any undesirable medical occurrence, in any dose, resulting in death, risk of death, situations requiring hospitalization or prolongation of existing hospitalization, significant or persistent disability, congenital abnormality, and clinically captive event.[38]	Serious: A noxious and unintended response to a drug or natural health product that occurs at any dose and that requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening, or results in death.[43]	Serious: Any undesirable medical occurrence, in any dose, resulting in death, risk of death, situations requiring hospitalization, or prolongation of existing hospitalization.[39]	Serious: When its outcome is death or a threat to life, or when it generates or prolongs hospitalization, causes disability, termination of pregnancy, or malformations.[40]	Serious: Any adverse reaction that causes death can lead to life-threatening requires hospitalization of the patient or prolonged existing hospitalization, causes significant or persistent disability, or constitutes a congenital disability or birth defect. For notification, all suspected transmission of an infectious agent through a drug.[41]	Serious: Any clinical manifestation that occurs with the administration of any dose of a medicinal product including vaccines, and that: Cause the death of the patient endangers the patient's life at the very moment they arise, makes it necessary to hospitalize or prolong hospital stay, cause for disability or permanent or significant disability, alterations or malformations in the newborn, is considered medically necessary.[44]	Serious: Drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/ birth defect.[28]
Severity	Not specified[37]	Not specified[38]	Not specified[43]	Not specified[39]	Not specified[40]	Mild, moderate, or severe[41]	Mild, moderate, or severe[44]	Not specified[28]
Minimum information	1. Start date of the adverse event 2. Date of commencement of administration of the suspected medication 3. Age of the patient 4. Full event description 5. Name of the drug or drugs involved (DCA – Argentine Nonproprietary Name – and brand)[37]	1. Identification of the notifier 2. Identification of the patient (name or initials; or sex; or age or date of birth) 3. Description of the adverse event 4. Name of the suspected drug[38]	1. An identifiable reporter (source) 2. An identifiable patient 3. A suspect product 4. An adverse reaction[43]	1. Individualizable patient 2. Identification of the suspected drug and the start and end date of its administration 3. Description of the suspected ADR, and its start date 4. Notifier information[39]	1. Individualizable patient 2. Identification of the suspected drug and the start and end date of its administration 3. Description of the suspected ADR, and its start date 4. Notifier information[40]	1. Identifiable notifier (name, address, and profession) 2. Identifiable patient (name or initials, medical history, sex, age, date of birth) 3. One or more suspicious drugs with batch and manufacturer 4. One or more suspicions of ADR 5. Start and end date of treatment 6. Start and end date of the reaction[41]	1. An identifiable patient/ consumer 2. At least one ADR or some other problem related to the use of the product 3. Suspicious medicinal products and 4. Notifier's details[42]	1. Patient information 2. Adverse drug experience 3. Suspect medical product 4. Initial reporter information 5. Applicant information[28]
Patient and Healthcare Professional confidentiality	Maintain the privacy of the patient transmitting a code and reporter.[37]	Maintain the privacy of the patient, healthcare professionals, and institutions, including personal identities and all personal medical information.[38]	Maintain the privacy of the patient and reporter.[43]	Maintain the privacy of the patient, by transmitting a code.[45]	Maintain the privacy of the patient and reporter.[40]	Maintain the privacy of the patient and reporter.[41]	Safeguard confidential patient and notifier information.[42]	Not include in reports the names and addresses of individual patients; include the name of the reporter from whom the information was received, even when the reporter is the patient.[28]
ADR terminology transmitted	International medical terminology accepted[37]	MedDRA[38,46]	MedDRA[43]	Not specified[39]	MedDRA[47]	MedDRA[41]	MedDRA[42]	MedDRA[28,48]

(Continued)

Table 3. (Continued)

ICSR postmarketing requirements	ANMAT (Argentina)	ANVISA (Brazil)	Health Canada (Canada)	ISP (Chile)	INVIMA (Colombia)	CECMED (Cuba)	COFEPRIS (Mexico)	FDA (United States)
Suspected drug product encoding terminology	WHODrug®[37]	WHODrug®[38]	DIN code[43]	Not specified[39]	WHODrug®[47]	Not specified[41]	WHODrug® (in the process of implementation)[42,49]	Only NDCs are required[28,48]
Reporting time frame	*Serious*: ADR within 15 calendar days. *Fatal or resulting in death risk*: Within 7 days. *Non-serious*: Bimonthly.[15,37]	*Serious ADR* (expected and unexpected) in no more than 15 calendar days. *The other cases* must be submitted within the PBRER. *Urgent situations* must be submitted in no more than 72 h.[38]	*Serious ADR* initial and follow-up (expected and unexpected) within 15 calendar days since receiving relevant information. *The other cases* must be submitted within the PBRER.[43,50]	*Serious ADR* from medicines whose marketing authorization is not having more than 5 years must transmit within 15 calendar days. *Other ADRs* that don' fulfill the above requirements must be submitted within 30 days. *Note*: MAH must submit the first 5 days of each month a report to ISP with all the ADR.[39]	*Serious and unexpected*: No more than 72 h. *Serious*: No more than 72 working hours. *Non-serious*: The last five working days of each 2 months, a report that contains, the ADRs that are expected and the non-serious ones and unexpected. MAH will be able to upload the events daily or during the bimester.[47]	*Serious ADR*: The first 24 h and no more than 72 h of knowing the event. *Serious ADR follow-up*: 30 calendar days. *Non-serious*: Send electronically every quarter.[41]	*Serious*: (a) Mortal: No more than 7 calendar days. (b) No-mortal: No more than 15 calendar days. (c) Two or more serious cases, similar in the same place, with the same medicinal product, and from the same batch Immediately not exceeding 48 h. Non-serious: Within 90 calendar days.[42]	*Serious and unexpected ADR*: Initial and follow-up 15 calendar days. *Serious and expected or non-serious*: Submit in quarterly intervals, for 3 years from approval, and then annually.[28]
Follow-up reports	Additional medical significant information and use in the pediatric population and pregnant or breastfeeding women.[37]	Additional medical significant information to elucidate causality.[38]	Additional medical significant information; prioritization of serious and unexpected, serious and expected, and non-serious and unexpected.[43]	Additional medical significant information.[39]	Additional medical significant information.[40]	Additional medical significant information.[41]	Additional medical significant information, use by pregnant or breastfeeding women, and more information are required for a better assessment.[44,51]	Additional medical significant information received or as requested by the agency.[28]
ICSR transmission	Electronically, by E2B XML and an online form, or physical form submitted by email.[37]	Electronically, *via* VigiMed submitting E2B XML archive or on the web form.[46]	Electronic reporting to the TPMO or non-electronic send CIOMS form by mail or fax.[43]	1. Electronic form on RED-RAM system 2. Physical form 3. Email[39]	Electronically, either E2B XML or online form.[47]	Expedited: Email or telephone Non-expedited: Electronically.[41]	1. e- Reporting Industry (E2B XML or online form). 2. Email. 3. Physical form.[42,51]	Electronically, either database-to-database or safety reporting portal.[48]

@WHODrug, International Reference for Medicinal Product Information.
The review of ICSR requirements among PAHO NRARs shows similarities such as the types of unsolicited reports during postmarketing, seriousness criteria, minimum information to be transmitted, confidentiality criteria, and ADR coding in the transmission of ICSRs by MAHs; on the other hand, there is a lack of harmonization such as the coding of products in the transmission of ICSRs by the MAHs, the times and criteria that determine the transmission (especially for expedited reports), follow-up requisites, the severity definition, and how they are transmitted.
ADR, adverse drug reaction; ANMAT, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica; ANVISA, Agencia Nacional de Vigilancia Sanitaria; CECMED, Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos; CIOMS, Council for International Organizations of Medical Sciences; COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios; DCA, Denominación Común Argentina; DIN, Drug Identification Number from Canada; FDA, US Food and Drug Administration; ICH, International Council for Harmonisation; ICSR, Individual Case Safety Report; INVIMA, Instituto Nacional de Vigilancia de Medicamentos y Alimentos; ISP, Instituto de Salud Pública; MAH, Marketing Authorization Holder; MedDRA: Medical Dictionary for Regulatory Activities; NDC, National Drug Code from USA; NRA, National Regulatory Authority; NRAR, National Regulatory Authority of Reference; PAHO, Pan American Health Organization; PBRER Periodic Benefit–Risk Evaluation Report; PIDM, Programme for International Drug Monitoring; TPMO, Trading Partner Management Office; XML, eXtensible Markup Language.

Table 4. PAHO's ICSR minimum information.

Requirements	Information to transmit[5]
Patient information	Weight, age, sex, and a brief medical history (where relevant); in some countries, ethnicity is required.
Adverse drug reaction description	Nature, location, and intensity, including the date of commencement of signs and/or symptoms, evolution, and outcome.
Suspected drug product information	Generic name or trademark, dosage, route of administration, start and end date of treatment, indication for use, expiration date, batch number, and manufacturer name.
Patient data relative to their disease	State of health before administration of the medicinal product, comorbidities, and history of relevant familial diseases.
Concomitant medication	All other medicinal products used by the patient (including self-medicated): names, dosages, routes of administration, and start and end dates of administration.
Information from the healthcare professional who reports	The name and address of the notifier should be considered confidential and only used to verify the data, till complete or follow-up on the case.

sion; compared across nine parameters, highlighting areas of disharmony across the regulation.

Postmarketing ICSRs

All NRARs transmit ICSRs in the postmarketing phase.[28,37,38,40–43,45] Nevertheless, the FDA and Health Canada require MAHs to send ICSR derived from websites and social networks.[28,52] Otherwise, CECMED is the only NRAR that requests at least a conditional causality relation (according to the causality algorithm of the Cuban PV system, which uses five categories: definitive, probable, possible, conditional, and unrelated) between ADR-medicinal products to carry out the transmission of the ICSR.[41]

Seriousness

Adopted by all NRARs, this requirement is a serious ADR that fulfills the following outcomes: death, life-threatening, caused or prolonged hospitalization, congenital anomalies, or causing disability.[28,38,40,41,44,45,52,53] Additionally, the term 'medically important', established by ICH is only adopted by four entities, ANVISA, Health Canada, COFEPRIS, and the FDA.[28,38,43,44]

Severity

The PAHO suggests the evaluation of the severity of ADRs, which determines if the ADR affects the patient's daily activities. Thus, be classified as mild, moderate, or severe.[5] Although for CECMED and COFEPRIS, it is a requirement part of the content of the ICSR,[41,44] this category is not considered by ICH.[53]

Minimum information

An identifiable patient, an identifiable reporter, an ADR, and a suspicious product are considered to be the minimum data harmonized by ICH.[11] These minimum data are also considered within the GPVP issued by the PAHO. However, both ICH and PAHO always encourage requesting additional information from the reporter (e.g. concomitant therapies, comorbidities, relevant clinical history) to improve its quality when transmitting an ICSR (Table 4).[5]

Patient and healthcare professional confidentiality

To protect the confidentiality of patients, health professionals, and caregivers, MAHs must ensure data privacy at the time of transmission of ICSRs to NRAs.[5,11] Consequently, all NRARs contemplate the confidentiality of information[28,40,41,44,45,52–54]; however, in the case of the FDA, MAHs must include the informant's name.[28]

ADR and suspected drug product terminology

As part of ADR coding, ICH and PAHO establish the use of MedDRA.[5,55] Some institutions such

as, ANMAT, ANVISA, Health Canada, INVIMA, CECMED, COFEPRIS, and FDA request ADR coding under MedDRA.[37,41,43,44,46,48,56] In contrast, the ISP does not requires the specific use of any medical dictionary.[39]

ICH suggests coding pharmaceutical products using WHODrug, which allows product traceability[57]; and is currently considered in the E2B R3.[34,58,59] In addition, WHODrug pharmaceutical coding by MAHs enables compliance with IDPM requirements, so its implementation is available in ANMAT, ANVISA, INVIMA, and COFEPRIS.[46,56,60,61] Nevertheless, Health Canada and FDA use their regional codification.[43,48] At the same time, ISP and CECMED do not define the use of any harmonized dictionary for coding medicinal products transmitted by MAHs.[39,41]

Reporting time frame

The periods for transmitting cases during the postmarketing phase by MAHs to NRAs, established in the ICH E2D guideline, contemplate two types of reports: expedited and non-expedited.[53]

Expedited report period. According to ICH, expedited reporting applies to all serious and unexpected ADRs (those whose nature or severity is inconsistent with the information described in the relevant documentary source – monograph, prescribing information, and summary of product characteristics).[62] This term specifically applies in Health Canada, CECMED, and FDA.[28,41,43] Moreover, Health Canada considers all serious cases in its territory.[43] CECMED additionally includes increased frequency expected serious ADRs and cases of counterfeit medicine.[41,63] Under ICH, this type of expedited report must be transmitted in a period not exceeding 15 days.[53]

Serious domestic cases, whether expected or not must be transmitted expedited within 15 days to ANMAT, ANVISA, Health Canada, ISP, and COFEPRIS.[37,38,42,43,45] On the other hand, the ISP grants a grace period of up to 30 days if the drug is not a new medicine.[39]

Regarding fatal or life-threatening ADRs, ANMAT and COFEPRIS request its transmission within the first 7 days, whereas ANVISA requires within the first 72 h. On the other hand, if two or more serious cases that occur in the same place, with the same product and batch COFEPRIS indicates only 48 h for transmitting.[37,38,42]

Non-expedited report period. In non-expedited reports, the ICH suggests its inclusion into the 'Periodic Benefit–Risk Evaluation Report (PBRER)' but are not transmitted to the ICSR.[53] Meanwhile, ANVISA and Health Canada, adhere to it. The ISP requests ICSR transmission monthly, ANMAT and INVIMA bimonthly, CECMED quarterly, COFEPRIS requests transmission up to 90 days starting from the date knowledge of the case and FDA requests in quarterly intervals for the first 3 years from approval and then, once annually.[28,37–39,41,42,47,50]

Follow-up reports

Once initial ICSRs are transmitted, MAHs should submit subsequent follow-up reports to determine new transmission criteria and causality, as PAHO suggests when incomplete reports are transmitted and serious or unexpected ADRs happen.[5] The NRARs adopted follow-up transmission per new medical information received (e.g. clinical information or complementary exams).[28,37,38,40,41,43,44,64]

Moreover, ANMAT requires from MAHs follow-up reports when pediatric, pregnant, and breastfeeding women transmit an initial ICSR,[37] whereas COFEPRIS only requires from MAHs the follow-up when pregnant and breastfeeding women present an ADR.[52]

Only FDA and Health Canada indicate a transmission timeline when follow-up reports were transmitted as expedited within 15 days.[28,42] On the other hand, ANMAT, ANVISA, CECMED, COFEPRIS, INVIMA, and ISP do not indicate a timeline for its transmission.[37,39,41,44,56,65]

ICSR transmission

ICSR transmission to NRARs by MAHs can be made in four different manners: (1) NRAR's official safety reporting portals submission: CECMED, ISP, and FDA permit transmission by entry information on electronic forms.[23,39,48] (2) e-Reporting (UMC) submission: ANMAT, ANVISA, INVIMA, and COFEPRIS allow it.[46,49,56,61] (3) XML-E2B submission: ANMAT, ANVISA, Health Canada, INVIMA, COFEPRIS,

and the FDA utilize it.[46–48,61,66] (4) Forms: ANMAT, Health Canada, ISP, CECMED, and COFEPRIS permit the transmission of ICSRs by official PDF forms.[39,41,43,45,51,67]

NRAR's PV national databases

Globally, the ADR database is managed by UMC under VigiBase; in a local view, every NRA database facility follows ICSR and assessment for signal detection.[68] The public availability of the ADR database is only obtainable by the FDA and Health Canada.[69,70] In contrast, Latin American databases are not publicly acquirable; in this case, comparing across countries is impossible.

To enhance the management and harmonization of ICSRs, the UMC offers the use of VigiFlow®,[54] a web-based system for managing PV databases for countries that require it, incorporating ICH guidelines compliment, offered in a low-cost way.[71] Nowadays, ANMAT, ANVISA, INVIMA, and COFEPRIS implement it as their national database.[46,49,56,61]

Discussion

As reviewed, all NRARs have a well-structured and adequately regulated ICSR transmission system, allowing them to satisfy the minimum requirements established by PAHO and ICH. Although ICH and PAHO seek harmonization for the transmission of ICSRs, there are still significant differences, such as:

1. Social media vigilance: Lack of regulation for the surveillance of social networks to detect possible ADRs, in this case, Health Canada and the FDA being the only NRARs that request the MAHs to execute this activity.
2. Expedited and non-expedited ICSRs: Transmission times vary from 48 h to 15 days in expedited cases. For example, COFEPRIS indicates different scenarios; first, if two or more serious cases occur in the same place, with the same product and batch, COFEPRIS indicates only 48 h for transmitting; second, fatal and life-threatening within 7 days like ANMAT. In fatal cases, INVIMA and ANVISA require transmission within 72 h (it should be noted that all the above scenarios could be expected or not). Only non-expected and serious cases are transmitted as expedited to CECMED and FDA; on the other hand, serious and expected or not cases are transmitted expedited by the other NRARs within 15 days. Differences in communication, some by PBRER and others by individual transmission in non-expedited cases.
3. Coding: Most NRARs allow MAHs to encode ADRs in MedDRA, except the ISP, while using WHODrug to code suspect drugs is still under evaluation.
4. Severity: The severity suggested by PAHO is only considered by CECMED and COFEPRIS as a component of the ICSRs.
5. Follow-up reports: ANMAT and COFEPRIS request follow-up reports when ADRs happen in pregnant and breastfeeding women; in addition, ANMAT request follow-up in pediatric cases FDA and Health Canada request follow-up reports only if the initial case was expedited. The rest of the NRARs do not mention follow-up cases timeline for its transmission.
6. ICSR transmission: ANMAT, ANVISA, Health Canada, INVIMA, COFEPRIS, and FDA allow XML transmission by MAHs.

Differences in harmonization around ICSR transmission are evident regarding timeline and transmission ways of submission, even considering the publication of the GVP in the Americas to harmonize the criteria and their implementation within every regulatory framework. A survey on a total of 19 countries reported that only three countries in the region adopted this document in its entirety (16%), four countries partially adopted it (63%), and four countries did not adopt it (21%).[14] Possible implications for the NRAs in the disharmony could address the volume, timeliness, accessibility, and workload for processing ICSRs.

Regulatory differences in PV activities have been previously reported by Hans *et al.*, where there are differences in the definitions and reporting requirements among agencies such as the FDA, the Medicines and Healthcare Products Regulatory Agency from the United Kingdom, the Central Drugs Standard Control Organization from India, and Health Canada, which affect the data in ICSRs of the same product that the MAHs submit to different NRAs.[4]

In relation to the NRAR's ICSR databases, only the FDA and Health Canada allow public access. The databases permit to see how the notifications are made by patients, health professionals, and caregivers. In Asia, the PV systems and databases differences among NRAs of Korea, Japan, and Taiwan, were reviewed by Kimura *et al.* in 2011. Some of the characteristics of spontaneous reporting systems in these countries include adherence to ICH E2B, the medical terminology used, and the public availability of ADR databases. From 2007 to 2009, a difference in the number of annual reports was observed, with Korea and Taiwan showing a notable increase. Although differences in health systems regulations and culture were evident among these countries, the authors identified that variations in professional training, sensitivity to adverse drug events, and reporting motives contribute to the quantity and quality of reporting.[72]

Although public availability of national databases is essential for different stakeholders (not only NRAs) to identify safety signals, this also implies some limitations such as: duplicate and incomplete reports, some reports without causality assessment, reports not medically confirmed, and incidence.[69,70] To investigate the magnitude of replication (ICSR submission to any recipient by MAH and then re-transmitted to other recipients), the variability and divergence, a global study by van Stakelenborg *et al.* in 2023 reflected how replication of ICSR is an existing phenomenon. First, the average number of recipients by case version was 3; second, 12.4% of the case versions were submitted to 10 or more NRAs, which let them conclude that the growth of safety information and 3 the lack of harmonization can result in data quality problems and impact public health as more ICSR transmission among MAHs to different NRAs is not necessarily an improvement, since there is regulatory disharmony and ICSR transmission, affecting the assessment and decision due differing clinical information among NRAs.[73]

Considering that the GPVPs dictate that NRAs must share their ADRs globally and send them to VigiBase, a 2020 report by the PAHO established that about half of the cases worldwide are transmitted through the Americas. However, less than 5% originates from Latin American agencies; from this proportion of ICSRs, the majority comes from NRARs (ANVISA, the one with more ICSRs transmitted) *versus* the rest of NRAs in America. NRARs in Latin America point out that this is due in an important way to the differences in the compatibility of national and VigiBase software; the main reason is that the data must be uploaded manually, limiting the number of reports shared to UMC.[8]

It has been reported how electronic ICSR transmission under ICH E2B has permitted a higher number of reports to be shared to VigiBase[8,9]; our review shows that FDA and Health Canada fulfill ICH requirements under their databases.[69,70] On the other hand, ANMAT, ANVISA, INVIMA, and COFEPRIS implemented recently the use of VigiFlow by UMC.[46,49,56,61] The implementation of VigiFlow by ANVISA was documented in 2020 by Vogler *et al.*, and their findings include how the ADR reporting led to a 62.6% increase between 2018 and 2019. About 100% of the ICSRs were sent to VigiBase in 2019 with a causality assessment compared with 10% in 2018. The improvement was attributed to training, promotion, and friendlier use for the people.[54]

Our findings regarding the differences in ICSR requirements suggest that every NRAR adopts international or regional requirements according to its resources, capabilities, and legislation. Since some NRARs, such as the FDA, Health Canada, INVIMA, and COFEPRIS, are members of ICH, harmonized criteria could be expected among them; however, it some requisites are still different. The differences might impact patient safety monitoring from a regional and global view since once ICSRs are transmitted by MAHs, the NRARs who share all this information to VigiBase in some cases if the ICSRs are not sent under E2B-XML form the workload increment, and missing reports would not be transmitted affecting the further evaluation. Further research is needed to understand how differences could affect VigiBase and the challenges with transmission across case types and report versions demonstrating the divergence between MAHs and NRAs. In addition, more work is needed to address the impact of drug safety assessment.

Conclusion

The transmission requirements of ICSRs comply with guideline E2B; however, considering the rise of electronic transmission, there is still work to be done for their implementation and harmonization, especially in Latin America. This might be

harmonized with the exact transmission timelines, XML-E2B transmission implementation for MAHs, use of harmonized codes, and same definitions. Foremost, the use of electronic ICSRs facilitates their tracking, and generation of containment measures by the NRARs, so the early identification of new ADRs, would allow the implementation of minimization activities in conjunction with the MAHs, contributing to the continuous assessment of the benefit–risk balance of medicines to ensure that they are safe for patient use.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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