TECHNICAL SPECIFICATION

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Health informatics — Electronic reporting of adverse drug reactions

Informatique de la santé — Reportage électronique des réactions défavorables de drogue

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

In other circumstances, particularly when there is an urgent market requirement for such documents, a technical committee may decide to publish other types of document:

— an ISO Publicly Available Specification (ISO/PAS) represents an agreement between technical experts in an ISO working group and is accepted for publication if it is approved by more than 50 % of the members of the parent committee casting a vote;

— an ISO Technical Specification (ISO/TS) represents an agreement between the members of a technical committee and is accepted for publication if it is approved by 2/3 of the members of the committee casting a vote.

An ISO/PAS or ISO/TS is reviewed after three years in order to decide whether it will be confirmed for a further three years, revised to become an International Standard, or withdrawn. If the ISO/PAS or ISO/TS is confirmed, it is reviewed again after a further three years, at which time it must either be transformed into an International Standard or be withdrawn.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO/TS 22224 was prepared by Technical Committee ISO/TC 215, *Health informatics*.

Introduction

This Technical Specification is considered to be an international guideline for developing and implementing the electronic system in which national or international organizations can receive and transfer ICSRs (individual case safety report) from healthcare professionals and/or consumers.

In this Technical Specification, ISO guidelines for electronic reporting of ADR are presented by describing business processes to be considered nationally and internationally in implementing ADR reporting systems with the modifications of the existing international guidelines of the following ICH documents:

— ICH E2B[6];

— ICH ICSR DTD Version 2.1.

Since ICH guidelines (E2B[6] and other revised documents) were well developed and are being adopted in the EU, US, Japan and other countries, there might be no need to develop the ISO guidelines independently from ICH. Since ICH guidelines have been developed for electronic transmissions of individual case safety information between pharmaceutical companies and regulatory bodies in ICH member countries, these do not fully reflect the needs of other non-member countries and also do not contain consumer perspectives in reporting processes.

From this point of view, the ISO working group has studied the ICH guidelines and developed the International Standards for electronic reporting of adverse drug reactions by modifying the existing ICH guidelines which all the member countries can use for implementing electronic reporting systems for ADRs.

Health informatics — Electronic reporting of adverse drug reactions

1 Scope

This Technical Specification encompasses the electronic reporting of adverse reactions caused by drugs for human uses. Thus, other businesses relating to adverse events caused by blood transfusions, medical devices and veterinary drugs are excluded from the scope of this Technical Specification.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

HL7/ANSI Approved ICSR standard in Domain, *Public Health Reporting*, 2002

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
adverse drug reaction
ADR
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 disease, or for the modification of physiological function

NOTE 1 This, as defined by the World Health Organization (WHO), is intended to govern the scope of standards.

NOTE 2 In the above definition, drug or medicine is defined as any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug or medicinal product is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information.

NOTE 3 There are many other terms that pertain to or are related to ADR, but should be differentiated from the definition of ADR such as in 3.2 and 3.3.

3.2
adverse event
adverse experience
any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment

3.3
side effect
any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to the pharmacological properties of the drug

3.4
ANSI
American National Standards Institute
first organization for fostering development of technology standards in the United States

NOTE ANSI works with industry groups and is the U.S. member to ISO.

3.5
drug
any chemical compound that may be used on or administered to humans or animals as an aid in the diagnosis, treatment or prevention of disease or other abnormal condition, for the relief of pain or suffering, or to control or improve any physiological condition

[Dorland's Illustrated Medical Dictionary, 27th edition]

3.6
DTD
document type definition
hierarchical organization or representation of the information contents of a document utilized by SGML

3.7
HL7
Health Level 7
ANSI standard used to facilitate the electronic interchange of data in a healthcare environment

3.8
ICH
international conference on harmonization of technical requirements for registration of pharmaceuticals for human use

3.9
ICSR
individual case safety report
healthcare report describing untoward incidents, therapeutic misadventures, iatrogenic injuries or other adverse occurrences directly associated with care delivery or services provided within the jurisdiction of a medical centre, outpatient clinic or other medical facility

3.10
interim reporter
professional or public organization that is monitoring, receiving and assessing ADR reports from health professionals and consumers and reporting significant ADRs to a regulatory authority in its own region

3.11
interoperability
degree or extent to which diverse environments (hardware and software) are able to exchange information without loss of content and in a manner transparent to the user

3.12
messaging
technology that enables messages to be sent by electronic mail

NOTE Messaging includes directory services, allows composition of the message and addressing and transfer over the network.

3.13
national pharmacovigilance centre
single, governmentally recognised centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety

3.14
non-proprietary drug (generic) name
drug name that is not protected by a trademark, usually descriptive of its chemical structure, sometimes called a public name

NOTE In the US, most generic drug names are assigned by the US Adopted Name Council (USAN). Other generic names in common use are the National Formulary (NF) and the US Pharmacopoeia.

3.15
product manufacturer
organization that is responsible for the manufacture of a product and is usually the entity that holds the marketing authorization for the product

3.16
receiver
intended recipient of the transmission

3.17
regulatory agency
regulatory authorities
agency/authorities responsible for regulating products used in health care

NOTE The agencies are collectively referred to as regulatory agencies.

3.18
reporter
primary source of the information (i.e., a person who initially reports the facts)

NOTE This should be distinguished from the sender of the message, though the reporter could also be a sender.

3.19
SNOMED clinical terms
SNOMED CT
clinical terminology maintained and distributed by the SNOMED International Authority under the editorial guidance of the SNOMED International Editorial Board

3.20
spontaneous reporting
system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority

3.21
sender
person or entity creating the message for transmission

NOTE Although the reporter and sender might be the same person, the function of the sender should not be confused with that of the reporter.

3.22
serious adverse drug reaction
adverse product reaction that is fatal (i.e. results in death) or is life threatening or requires hospitalization or prolongation of a hospitalization or results in persistent or significant disability/incapacity or results in a congenital anomaly/birth defect

3.23
SGML
standard generalized markup language
ISO standard metalanguage for describing structured information in a platform independent manner

3.24
standard
technical specification that addresses a business requirement, has been implemented in viable commercial products and, to a practical extent, complies with recognised standards organizations such as ISO

3.25
XML
extensible markup language
subset of SGML that is completely compatible with SGML thereby allowing generic SGML to be served, received and processed on the web in the way that is now possible with hypertext markup language (HTML)

4 Business processes in ADR reporting

4.1 Setting up a pharmacovigilance centre

The reporting of adverse reactions to a central authority is required in many countries. The form and content of such reports could be standardized. There are many national examples of electronic reporting on which an International Standard could be based. The mechanism and process of adverse reaction reporting may be in the hands of agencies, e.g. Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, the European Agency for the Evaluation of Medicinal Products (EMEA) for the EU, the Federal Drug Administration (FDA) in the USA.

Internationally, the WHO is collecting ADR reports from many member countries through its collaborating centre of the Uppsala Monitoring Centre (UMC).

The number of national centres participating in the WHO International Drug Monitoring Programme has increased from 10 in 1968 to 67 in 2002. WHO is indicating that the national pharmacovigilance centres have played a significant role in increasing public awareness of drug safety and many national and regional centres are housed within hospitals, medical schools or poison and drug information centres, rather than within the confines of a drug regulatory authority.

In HL7 version 2.5, the flow of product experience information is described as in Figure 1, stating that "regardless of who originates a drug experience report, documentation of the experience eventually reaches the regulatory agencies. The manufacturer is mandated to alert the regulatory agency."

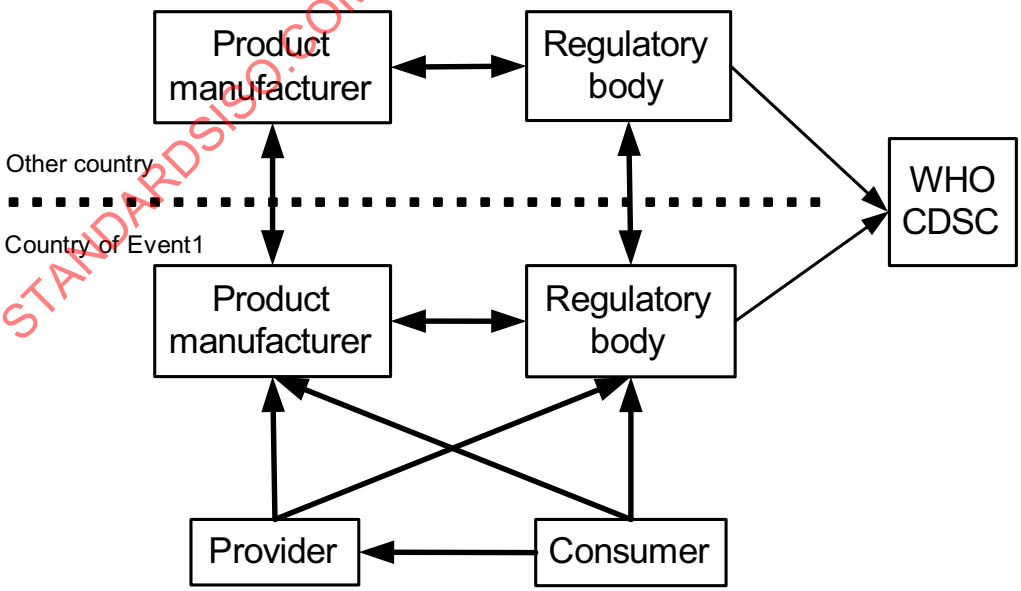


Figure 1 — Flow of product experience information

It is ISO's view that the ADR information should be collected from all possible reports of consumers, healthcare providers and manufacturers, by the national or regional pharmacovigilance centre of each country, but ultimately reach the national regulatory agencies and all the significant reports should be communicated to the WHO who can then disseminate the information internationally.

4.2 Setting up a reporting system of adverse drug reactions

There may be various reporting systems depending on reporters and the authority's policy.

There are three optional reporting systems according to reporters: reporting systems from consumers, healthcare professionals and manufacturers. Also, there are two types of reporting options: voluntary and mandatory. However, most authorities require voluntary reporting from consumers and healthcare professionals and mandatory reporting from the drug manufacturers. The format and contents of reporting systems from the consumers appear on the FDA's site (MEDWATCH[13]), the UK's Yellow Card Scheme[12] (www.yellowcard.gov.uk) and other authorities' sites.

Thus, it may be assumed there are four types of reporting systems as follows:

— voluntary reporting system from consumers;

— voluntary reporting system from healthcare professionals;

— mandatory reporting system from healthcare professionals;

— mandatory reporting system from drug manufacturers.

ICH guidelines (E2BM[7], ICSR DTD Version 2.1) describe well the technical requirements for electronic reporting of ADR and are utilized for developing web-based reporting systems in the member countries.

For example, the FDA has developed an online adverse event reporting programme through MedWatch and encouraged voluntary reporting from consumers and health professionals and mandatory reporting from drug manufacturers, distributors, and packers. In the programme, the electronic transmission of ICSR can be done by filling in the pre-designed report form (FDA Form 3500 and Form 3500A) in the PDF format.

The report form can be delivered to the FDA by various means of faxing and e-mailing. In the UK's Yellow Card Scheme, the reporters can fill in the ADR information on the web-based interface and electronically submit the ICSR. Other countries have developed reporting systems similar to the FDA MedWatch and UK's Yellow Card.

Though there may be significantly different considerations in encouraging the reporting from the consumers, many authorities do not have the separate reporting interfaces specifically designed for consumers. Consumers are experiencing ADRs and may be willing to report the events by themselves with or without help from health professionals, but may not understand the terminology in the reporting forms.

There may be a need for developing a separate form for consumers. In this case, there should be an additional reporting route other than the traditional reporting routes (between reporters and receivers). For this, it may be ideal to define the intervening organization (or interim reporter) and insert its identity in the process of ADR reporting as is shown in Figure 2.

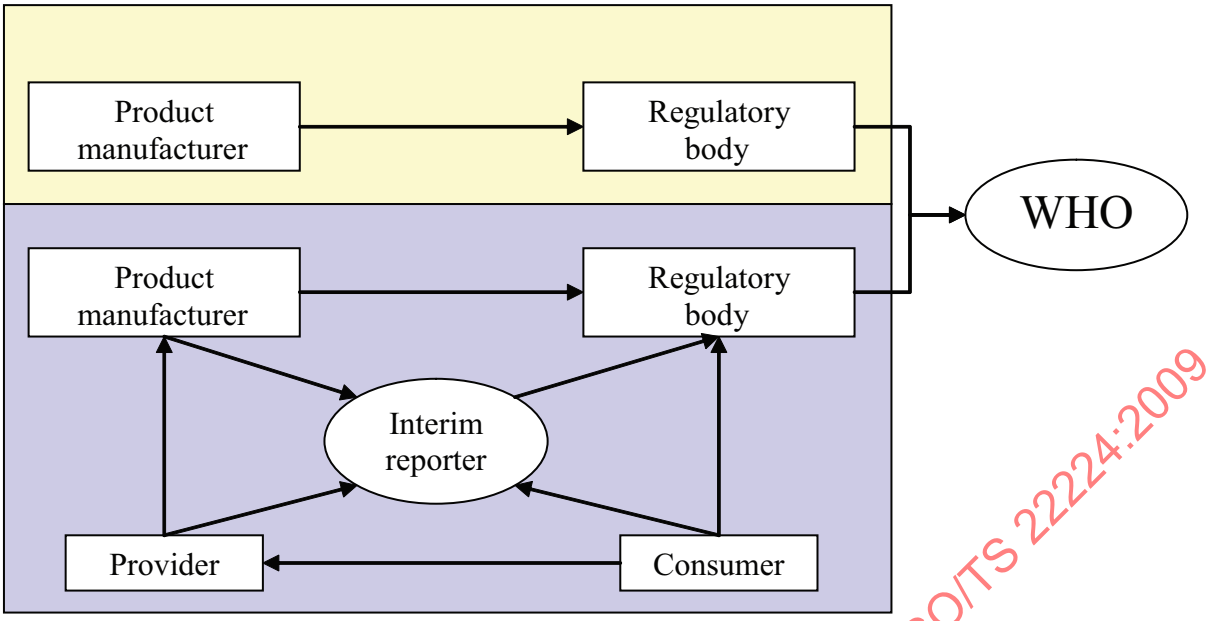


Figure 2 — Flow of ADR reporting information

In some countries (France, Korea etc.) regional pharmacovigilance centres other than national authorities have been established to improve under-reporting of ADR in their own countries. This may be one of typical bodies of interim reporters for ADR reporting.

In Figure 2 the following terminology and functions or roles of interim reporter may be considered.

a) Terminology for the organization between consumers and authorities:

- primary reporter (consumers or others);
- interim reporter will be used hereafter;
- receiver (governmental authority).

b) Functions and roles:

- encourage and facilitate ADR reporting from the consumers;
- help the consumer to report the ADR by assisting and consulting;
- relay the ADR reports to governmental authorities;
- ensure the ADR reports are utilized for the safety concerns of the consumers.

5 Modification of ICH guideline (E2BM) for implementing electronic reporting of ADRs

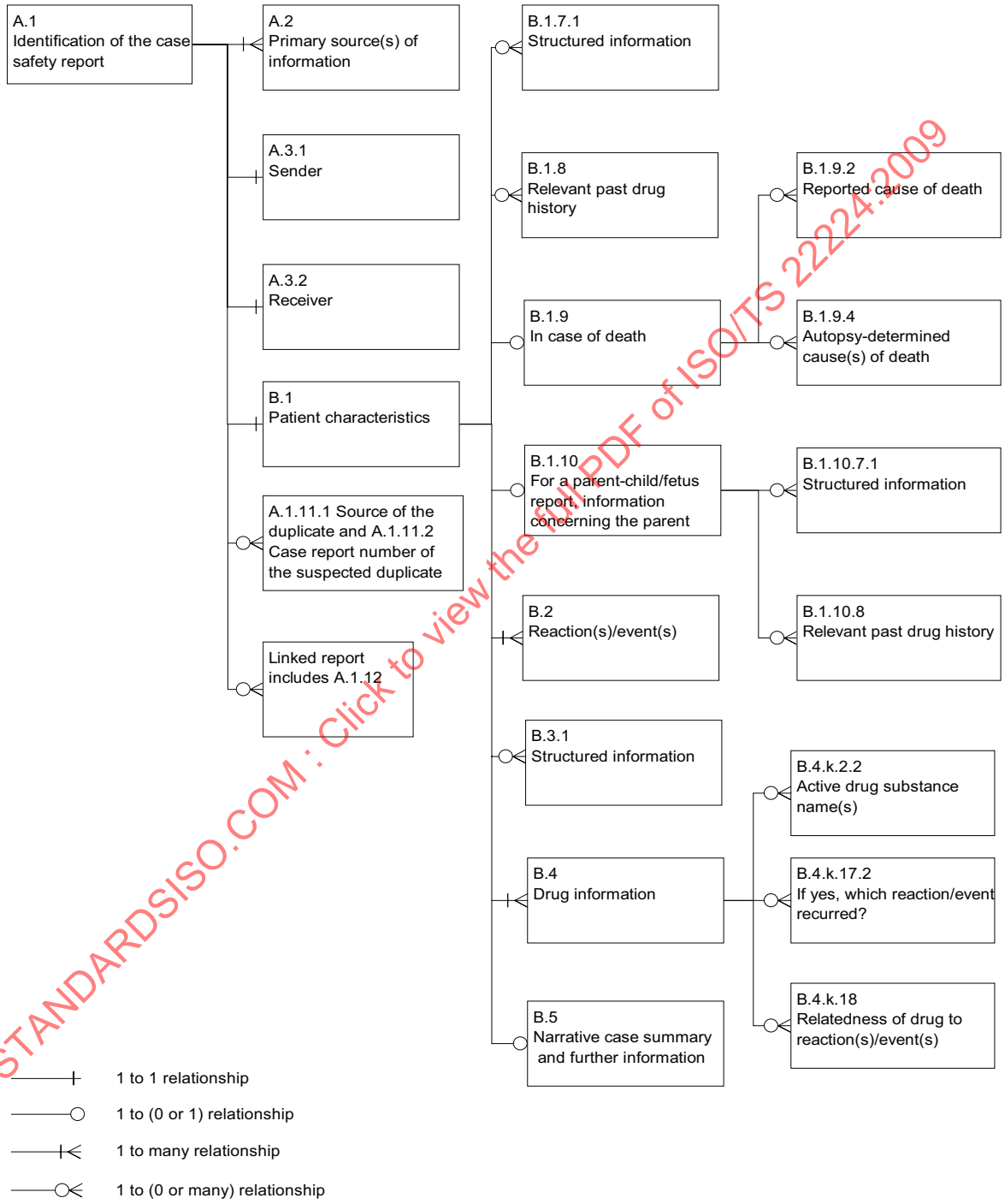
If the organization, as an interim reporter, is recognised by a national authority, the following relational view of data elements (M2 Relational View of E2B Data Elements) would be modified by inserting the interim reporter between A.2 or A.3.1 and A.3.2 (Receiver). See Figure 3.

If one determines to implement the electronic reporting system for the interim reporter, most parts of the ICH guidelines may be used as the components of ISO standards except for the following considerations.

- Modifying the reporting routes for consumers and the interim reporter.

— Modifying the attributes and DTD components for modern trends in information communication (such as mobile information communication via cellular phone).

— Adding more functional specifications or guidelines for assessing and utilizing ADR reports nationally and internationally and ADR vocabularies.



NOTE The text in the boxes refers to the attributes within each entity.

Figure 3 — M2 Relational View of E2B Data Element

Reviewing ICH guidelines, the parts of ICSR attribute list and DTD that should be revised are sampled as the following.

1) ICSR Attribute List (to be revised)

Data element	Title	Description	Field length	Field value	DTD descriptor
A.3.1.4k	Sender's fax number	Fax country code	3AN		senderfaxcountrycode
A.3.1.4l	Sender's e-mail address	E-mail address	100AN		senderemailaddress
A.3.1.4m	Sender's mobile number	Mobile phone number	10AN		sendermobilenumber
A.3.1.4n	Sender's mobile number	Mobile country code	3AN		sendermobilecountrycode
A.3.2.2a	Receiver identifier	Receiver organization	60AN		receiverorganization
A.3.2.2b	Receiver identifier	Receiver department	60AN		receiverdepartment
A.3.2.2c	Receiver identifier	Title	10AN		receivertitle
A.3.2.2d	Receiver identifier	Given name	35AN		receivergivename
A.3.2.2e	Receiver identifier	Middle name	15AN		receivermiddlename
A.3.2.2f	Receiver identifier	Family name	35AN		receiverfamilyname
A.3.2.3a	Receiver's Address	Street address	100AN		receiverstreetaddress
A.3.2.3b	Receiver's Address	City	35AN		receivercity