INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH E2B(R3) EXPERT WORKING GROUP /
IMPLEMENTATION WORKING GROUP**

APPENDIX I (B) TO THE IMPLEMENTATION GUIDE FOR ELECTRONIC TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS (ICSRS)

BACKWARDS AND FORWARDS COMPATIBILITY RECOMMENDATIONS

Version 2.03

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1.0 PURPOSE

This document is an appendix to the Implementation Guide (IG) for the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Electronic Transmission of Individual Case Safety Reports (ICSRs)'.

This Appendix is intended to assist reporters and recipients (including pharmaceutical companies, authorities and non-commercial sponsors) in implementing systems with special focus on the recommendations for conversion back and forth between the previous standard, i.e., E2B(R2) and this standard, i.e., E2B(R3).

The evolution of the guideline, from E2B(R2) to E2B(R3), has the consequence that ICSRs cannot be perfectly converted from one standard version to the other (either backwards or forwards). Repeated conversion could result in transformation or loss of information. Therefore receivers need to evaluate contents carefully. This document presents the recommendations for conversion agreed within ICH so as to provide a reference to system providers, and a common understanding on the way to convert ICSRs and ICSR acknowledgments (ICSR ACKs) between E2B(R2) and E2B(R3).

2.0 BACKGROUND

The current pharmacovigilance databases are operating largely on the basis of the ICH E2B(R2) guideline and the DTD version 2.1. Whilst it is envisaged that ICH E2B(R3) will improve the current standards, it is obvious that there will be a time of transition until all stakeholders (regulators, pharmaceutical industry and other parties in the pharmaceutical business sector) have implemented the new guideline and have their pharmacovigilance databases adapted to these new standards.

This implies that pharmacovigilance databases operating ICH E2B(R2) and / or ICH E2B(R3) standards will have to coexist and mapping procedures must be in place to ensure a coherent and harmonized exchange of ICSRs among all stakeholders at the international level. This is even more important since the exchange of ICSRs takes place between multiple senders and receivers and therefore depends on the implementation status (E2B(R2) or E2B(R3)) of each party in each transmission.

As a result, it is of major importance to address the compatibility between the two guidelines and the relevant message specifications and to provide a mapping standard that will ensure a smooth transition phase.

The present appendix intends to

- describe the need for a harmonized and documented backwards and forwards compatibility
- define the method to address compatibility issues
- categorize the compatibility issues
- define the mapping recommendations for the ICH E2B(R2) and the ICH E2B(R3)

3.0 COMPATIBILITY

3.1 Definitions

3.1.1 Compatibility

Different systems (e.g., programs, file formats, protocols, programming languages) that can work together or exchange data are said to be compatible.

For ICH E2B, compatibility refers to different pharmacovigilance systems (e.g., programs, file formats, protocols, programming languages) that can interact to support the electronic exchange of pharmacovigilance data on the basis of the ICH E2B(R2) and ICH E2B(R3) and applicable message specifications.

3.1.2 Backwards Compatibility

Backwards compatibility in the context of this appendix covers the capability to map the data elements of the ICH E2B(R3) guideline to the previous version, i.e., the ICH E2B(R2) guideline dated February 2001. The backwards compatibility should ensure that the integrity of the data is maintained and that limitations are fully described and supported by the E2B community (e.g., in case some data is lost during the conversion).

3.1.3 Forwards Compatibility

Forwards compatibility in the context of this appendix covers the capability to map the data elements of the ICH E2B(R2) guideline dated February 2001 to the new version i.e., ICH E2B(R3). The forwards compatibility should ensure that the integrity of the data is maintained and that limitations are fully described and supported by the E2B community (e.g., in case some data is lost during the conversion).

3.2 Compatibility Use Cases

3.2.1 Assumptions

Compatibility applies to pharmacovigilance systems and their capability to handle the message specifications in ICH E2B(R2) and ICH E2B(R3) formats.

It is assumed that the stakeholders will always send the reports in the format supported by their own pharmacovigilance system. The receiver of a case safety report is the only one who might be called upon to perform a conversion (either backwards or forwards) in order to load the report into his / her system.

Here is the list of assumptions made in the context of the present appendix:

- Pharmacovigilance systems that currently support the E2B(R2) format will continue to receive E2B(R2)-compliant messages, and there is no guarantee that these systems will immediately evolve to directly support E2B(R3)-compliant messages.

- Pharmacovigilance systems that are developed to support the E2B(R3) format will support E2B(R3) compliant messages and there is no guarantee that these systems will also be developed to support E2B(R2) messages. However, system developers are encouraged to provide backwards compatibility support.

- Pharmacovigilance systems should be built to process ICH message specifications. This implies that the underlying information model (usually the database) should be compatible with the ICH information model of the safety and acknowledgment messages. However, it is expected that national or regional requirements that govern system development might be outside the scope of the ICH information model, and therefore these recommendations for conversion might be extended to cover such additional requirements.

- Pharmacovigilance systems should be fully validated to ensure that the information exchanged in the ICH message format can be appropriately processed and stored in computer and human readable format.

3.2.2 Exchange Use Case

When exchanging ICH E2B messages between a sender and a receiver, the message can be created and processed by systems running either the ICH E2B(R2) or the ICH E2B(R3) specifications. In such situation, there is a need to convert the file from E2B(R3) to E2B(R2) or vice versa.

The conversion will always occur on the receiver side, i.e., just before loading the case into the pharmacovigilance system.
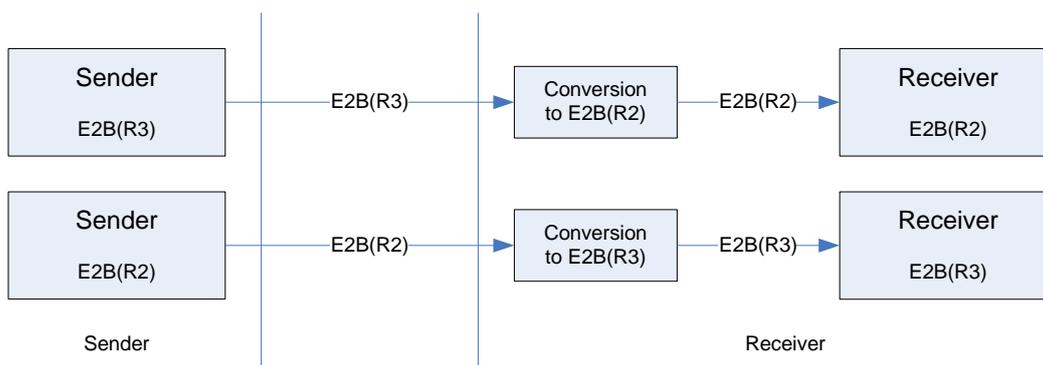
Figure 1: Use Case for Exchange

In order to properly be treated by the receiver's system, the message should be converted from the format used by the sender to the one in use by the receiver. The objective of this conversion is to retrieve all the relevant information at the receiver's side:

- Conversion from E2B(R3) to E2B(R2) calls for the retrieval of all the relevant E2B(R2) data elements and their content from the E2B(R3) format and mapping them to the E2B(R2) message format to generate an E2B(R2)-compliant message.

- Conversion from E2B(R2) to E2B(R3) calls for the generation of a new message format. This is accomplished by mapping the E2B(R2) data elements and their content to the E2B(R3) format. Note that some E2B(R2) information might not be available to map to E2B(R3) and therefore the new E2B(R3) formatted message should support the absence of information.

3.2.3 Retransmission Use Case

Based upon pharmacovigilance reporting requirements, E2B messages can be retransmitted between different senders and receivers. During this retransmission process, information previously submitted about the case should not be omitted or changed if no new information is available for retransmission. Recommended exceptions are listed in the E2B(R3) Specifications; these exceptions concern information available in both E2B(R2) and E2B(R3) information models.

The retransmission use case is described in the diagram below.
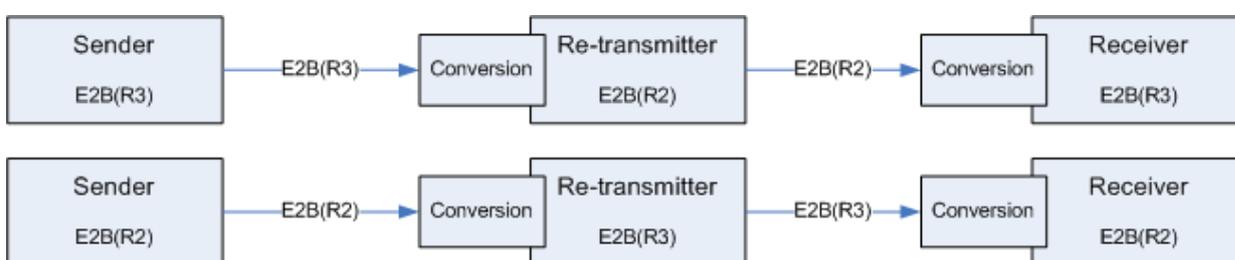
Figure 2: Use Case for Retransmission

In such case, the conversions should ensure data integrity as much as possible, i.e., with limited loss of information. Ideally, the initial and retransmitted messages should be identical from a content perspective except for the information updated by the re-transmitter.

This appendix intends to provide the recommended rules to follow regarding the conversion of E2B messages (backwards and forwards) including the capabilities regarding the retransmission use case, and known limitations.

3.3 Ensuring Data Integrity During E2B(R2) and E2B(R3) Conversions

The conversion use cases call for limiting the amount of data lost during the conversion process.

Conversion from E2B(R2) to E2B(R3) might result in some information being absent from the E2B(R3) formatted message because some of the data elements in E2B(R2) are no longer supported in E2B(R3), e.g., information on the receiver. Conversion from E2B(R3) to E2B(R2) should provide an abbreviated version of the data content because some data elements in E2B(R3) have been modified to increase the size of the text field, e.g., the sender's comments.

To minimize data lost during conversions, the following principles have been taken into account:

- If a data element in E2B(R2) is not present in E2B(R3), this implies that related information might not be considered required and therefore this information can be omitted. For example, the information about the receiver in E2B(R2) has been removed in E2B(R3).

- If a data element has been added in E2B(R3), this does not imply that current E2B(R2)-compliant systems would support the new information and therefore it is not always called for to convert the data to E2B(R2). However, the most important information will be converted to E2B(R2) as part of the case narrative section.

- For the retransmission use case where re-transmitters manage several conversions between E2B(R2) and E2B(R3), re-transmitters parse the content of the case narrative section of E2B(R2) in order to reconstruct the E2B(R3) message as close as possible to the original message.

The case narrative section of E2B has originally a limited size (20,000 characters). It is recommended to amend E2B(R2) system and design E2B(R3) systems so as to support the case narrative section with no size limitation. This would allow the use of the case narrative placeholder to store the fields that cannot be converted directly, i.e., at the location where the fields appear in E2B.

If the E2B(R2) system cannot be amended to remove the size limitation on the case narrative field, it is then recommended to extract the information out of the case narrative field into an external file, for the information part coming from the conversion process.

4.0 APPROACH FOLLOWED BY THIS APPENDIX

The Implementation Guide for the E2B(R3) message provides technical recommendations on the way to encode the new E2B information model using the XML Schema of the ICH ICSR message.

Therefore, the information fields that have not been amended in the new specification can be converted by following the same recommendations as the one provided in the Implementation Guide. The present appendix focuses on changes provided by E2B(R3), and for each change, or change type, guidance is provided regarding the way to convert the information backwards and forwards.

Changes provided by E2B(R3) can be categorized as follows:

- Date format: the E2B(R2) guideline supports dates with 2 separate fields, one for the date itself and one for the date format. The implementation of the E2B(R3) message has taken

another approach by supporting the date data type, i.e., with both date value and date format in the same field. Guidance is provided on the conversion of dates.

- Code mapping: E2B(R2) and E2B(R3) provide sets of codes for several fields. In some case, one format has additional code values than the other. Guidance is provided on the conversion of codes.

- Deletion: some fields of E2B(R2) have been deleted in E2B(R3). Guidance is provided on the way to handle such fields.

- Addition: some fields have been added in E2B(R3). Guidance is provided on the way to handle such fields.

- Field length: some fields have been extended (i.e., increased field length) in E2B(R3). Guidance is provided on the conversion of such fields.

- Masking: E2B(R3) provides another way to mask information, for privacy purposes, or because information is unknown. Guidance is provided on the way to pass from one encoding to the other, and vice versa.

- Structure: E2B(R3) provides another way to structure the information that was available in E2B(R2) guideline. Guidance is provided on the way to pass from one structure to the other, and vice versa.

The next section provides the guidance for conversion. The section has been organized per type of change, as to provide generic guidance before instructions specific per field, for both the ICSR and the ICSR Acknowledgement messages.

5.0 GUIDANCE FOR CONVERSION

5.1 Date Format

The E2B(R2) guideline supports dates with 2 separate fields, one for the date itself and one for the date format. For each field, the list of supported formats is specified in the guideline.

The implementation of the E2B(R3) message has taken another approach in supporting the date type, i.e., with both date value and date format in the same field. E2B(R3) only defines a minimal precision, and dates should be reported with the appropriate precision. In E2B(R3), dates can be reported with a time zone.

Guidance is provided on the conversion of dates, which depend on whether E2B(R3) supports the same date precision as E2B(R2), or whether additional formats are supported, with more or less precision.

5.1.1 Same Precision

All the date fields, except E2B(R2) A.1.3 / E2B(R3) C.1.2 (see section 5.1.4), can be expressed in a format that is appropriate for E2B(R2) and E2B(R3).

In such case, the following conversion recommendation should apply:

- To upgrade to E2B(R3), the date value should be copied from the date field of E2B(R2) into the field of E2B(R3). The date format field of E2B(R2) should be ignored.

  Example: Input in E2B(R2):   date value: 20081025; date format: CCYYMMDD

  Output in E2B(R3):   date field: 20081025

- To downgrade to E2B(R2), the date value should be copied from the field of E2B(R3) into the date field of E2B(R2), and, based on the number of characters, the date format should be detected and pasted into the date format field.

  Example: Input in E2B(R3):   date value: 20081025

  Output in E2B(R2):   date field: 20081025; date format: CCYYMMDD

5.1.2 Less Precision in E2B(R3)

For several date fields, E2B(R3) supports the same or lower precision than in the E2B(R2) guideline. Conversion guidance is only called for when a date is encoded with low precision in E2B(R3). The following fields can be encoded in E2B(R3) with precision to the year, while the E2B(R2) guideline expects a precision to the month or the day:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Date of birth (patient)	B.1.2.1	CCYYMMDD	D.2.1	at least to the day
Last menstruation period date (patient)	B.1.6	CCYYMM CCYYMMDD	D.6	at least to the year
Date of birth (parent)	B.1.10.2.1	CCYYMMDD	D.10.2.1	at least to the year
Last menstrual period date (parent)	B.1.6	CCYYMMDD	D.10.3	at least to the year

In such a case, the following conversion recommendation should apply:

- To upgrade to E2B(R3), the date value should be copied from the date field of E2B(R2) into the field of E2B(R3). The date format field of E2B(R2) should be ignored.

  Example: Input in E2B(R2): date value: 20081025; date format: CCYYMMDD

  Output in E2B(R3): date field: 20081025

- To downgrade to E2B(R2), the closest date format available in E2B(R2) should be selected, i.e., the lowest possible date precision of E2B(R2) for the field. The date value should be copied from the E2B(R3) field and completed with the additional digits set to default values, i.e., 01 for months and days, and 00 for hours, minutes and seconds.

  Example: Input in E2B(R3): date value: 2008

  Output in E2B(R2): date field: 2008; date format: CCYY

5.1.3 More Precision in E2B(R3)

For all the date fields, E2B(R3) supports the same or higher precision than in the E2B(R2) guideline. All the date fields can be encoded in E2B(R3) with a precision below the second (format CCYYMMDDhhmmss.uuuu), while the E2B(R2) guideline expects a precision to the year, the month, the day, the minute or the second (formats CCYY, CCYYMM, CCYYMMDD, CCYYMMDDhhmm or CCYYMMDDhhmmss).

In such case, the following recommendation applies:

- To upgrade to E2B(R3), the date value should be copied from the date field of E2B(R2) into the field of E2B(R3). The date format field of E2B(R2) should be ignored.

  Example: Input in E2B(R2): date value: 20081025; date format: CCYYMMDD

Output in E2B(R3): date field: 20081025

- To downgrade to E2B(R2), the following cases can occur:

    1) If the date format used in E2B(R3) exists in E2B(R2), see section 5.1.1.

    2) If the date format used in E2B(R3) does not exist in E2B(R2), the closest date format available in E2B(R2) should be selected, i.e., the highest possible date precision of E2B(R2) for the field. The date value should be copied from the E2B(R3) field and truncated to fit the date format of E2B(R2).

    Example: Input in E2B(R3): date value: 20081025093512.1234

    Output in E2B(R2): date field: 20081025; date format: CCYYMMDD

5.1.4 Date of this Transmission

In the context of the backwards and forwards compatibility, the field C.1.2 (i.e., the date of this transmission) is also used to carry information on the safety report version number (which is only available in the E2B(R2) message format).

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Safety report version number		2AN	-	-
Date of this transmission	A.1.3	CCYYMMDD	C.1.2	CCYYMMDDhhmmss

In E2B(R2), the safety report version number may be used to distinguish the evolution of the same safety report over time. In E2B(R3), this distinction is supported with the field C.1.2 which timestamps the case safety report down to the second. In E2B(R2), the field A.1.3 has precision to the day only.

To retain the versioning of case safety report, the following recommendation applies:

- To upgrade to E2B(R3), the date value of C.1.2 should be copied from the date field of E2B(R2) into the field of E2B(R3). The safety report version number, which is a number assumed to always remain below 60, should be appended to the field C.1.2 as seconds.

    Example: Input in E2B(R2):   date value of A.1.3: 20081025

    safety report version number: 3

    Output in E2B(R3): date value of C.1.2: 20081025000003

- To downgrade to E2B(R2), the date value of C.1.2 should be truncated to the day (see section 5.1.3) and the safety report version number should not be set. If the safety report version number is to be populated, the downgrade recommendations should be extended so as to support the batch conversion of ICSR messages, taking into account the sequence

of safety reports. Whether this is to be provided depends on the national / regional pharmacovigilance systems, and the related mechanisms are not described in this document.

5.1.5 Time Zones

For all the date fields, E2B(R3) supports the provision of a time zone at the end of the date format (CCYYMMDDhhmmss.uuuu±ZZzz). The E2B(R2) guideline does not support time zones.

In such case, the following recommendation applies:

- To upgrade to E2B(R3), the date value should be copied from the date field of E2B(R2) into the field of E2B(R3). The date format field of E2B(R2) should be ignored. No time zone should be defined when copying the date to E2B(R3):

  Example: Input in E2B(R2): date value: 200810250935; date format: CCYYMMDDHHMM

  Output in E2B(R3): date field: 200810250935

- To downgrade to E2B(R2), the time zone should be ignored:

  Example: Input in E2B(R3): date value: 200810250935+06

  Output in E2B(R2): date field: 200810250935; date format: CCYYMMDDHHMM

If, in addition to a time zone, the date has less or more precision in E2B(R3), then the recommendations defined in sections 5.1.2 and 5.1.3 also apply.

5.2 Code Mapping

E2B(R2) and E2B(R3) provide sets of codes for several fields. In some case, one version of the standard has more code values than the other.

Guidance is provided on the conversion of codes, which depend on whether E2B(R3) supports the same codes or whether additional code values have been introduced.

5.2.1 Coded value set

A. E2B(R2) and E2B(R3) expect the same set of codes for the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	Code List	Field	Code List
Type of report	A.1.4	4 possible values	C.1.3	4 possible values
Are additional documents available?	A.1.8.1	yes / no	C.1.6.1	true / false (+)
Does this case fulfil the local criteria for an expedited report?	A.1.9	yes / no	C.1.7	true / false (*)(+)
Other case identifiers in previous transmissions	A.1.11	yes	C.1.9.1	true (*)(+)
Qualification (primary source)	A.2.1.4	5 possible values	C.2.r.4	5 possible values (*)
Study type in which the reaction(s) / event(s) were observed	A.2.3.3	3 possible values	C.5.4	3 possible values
Continuing (patient medical history)	B.1.7.1d	3 possible values	D.7.1.r.3	3 possible values (*)
Was autopsy done?	B.1.9.3	3 possible values	D.9.3	3 possible values (*)
Continuing (parent medical history)	B.1.10.7.1d	3 possible values	D.10.7.1.r.3	3 possible values (*)
More information available (tests)	B.3.1.3	yes / no	F.r.7	true / false

In such case, the following recommendation applies:

- To upgrade to E2B(R3), the field value should be copied from the E2B(R2) field into the E2B(R3) field. The effective encoding of the code value should follow the guidance set in the related Implementation Guide.

- To downgrade to E2B(R2), the field value should be copied from the E2B(R3) field into the E2B(R2) field. The effective encoding of the code value should follow the guidance set in the related Implementation Guide.

B. E2B(R2) and E2B(R3) expect the same terms, however the codes may differ.

Description	E2B(R2)		E2B(R3)	
	Field	Code List	Field	Code List
Outcome of reaction / event at the time of last observation	B.2.i.8	6 possible values	E.i.7	6 possible values
Action taken with the drug	B.4.k.16	6 possible values	G.k.8	6 possible values

The fields that are marked with an asterisk (*) represent fields that can be nullified in E2B(R3). In such cases, the following downgrade recommendations apply:

- If the field is nullified as 'unknown' and an 'unknown' code is available in the code list of E2B(R2) for that field, the E2B(R2) field should be set to the code corresponding to 'unknown'.

- If the field is nullified as 'unknown' but no 'unknown' code is available in the code list of E2B(R2) for that field, the E2B(R2) field should not be set.

- If the field is nullified as another way (e.g., 'masked'), the E2B(R2) field should not be set.

The fields that are marked with a plus sign (+) represent fields that are required in E2B(R3) and optional in E2B(R2). In such case, the following upgrade recommendations apply:

- If the E2B(R2) field is set, the mapping should apply as described above.

- If the E2B(R2) field is not set, the E2B(R3) field should beset as follows:

    1) Field C.1.6.1 should be set to 'false'.

    2) Field C.1.7 should be set with a null flavour of type 'NI'.

    3) Field C.1.9.1 should be set with a null flavour of type 'NI'.

5.2.2 Report Nullification / Amendment

E2B(R2) and E2B(R3) expect different codes for the report nullification / amendment:

Description	E2B(R2)		E2B(R3)	
	Field	**Code List**	**Field**	**Code List**
Report nullification / amendment	A.1.13	▪ **Yes**	C.1.11.1	▪ **nullification** ▪ **amendment**

The following recommendation applies:

- To upgrade to E2B(R3), the following cases can occur:

    1) If the field value of E2B(R2) is set to 'yes', the field of E2B(R3) should be set to the code 'nullification'. The effective encoding of the code value should follow the guidance set in the related Implementation Guide.

    2) If the field value of E2B(R2) is not present, the field of E2B(R3) should not be provided in the upgraded message.

- To downgrade to E2B(R2), the following cases can occur:

    1) If the field value of E2B(R3) is set to 'nullification', the field of E2B(R2) should be set to the code 'yes'.

2) If the field value of E2B(R3) is set to 'amendment', the field of E2B(R2) should not be provided and the following information should be appended to the case narrative section (B.5.1):

> NULLIFICATION / AMENDMENT: Amendment: <content of field C.1.11.2: reason for nullification / amendment>

3) If the field value of E2B(R3) is not present, the field of E2B(R2) should not be provided in the downgraded message.

5.2.3 Sender Type

E2B(R2) and E2B(R3) expect different codes for the sender type:

Description	E2B(R2)		E2B(R3)	
	Field	**Code List**	**Field**	**Code List**
Sender type	A.3.1.1	▪ pharmaceutical company ▪ regulatory authority ▪ health professional ▪ regional pharmacovigilance center ▪ WHO collaborating center… ▪ other	C.3.1	▪ pharmaceutical company ▪ regulatory authority ▪ health professional ▪ regional pharmacovigilance centre ▪ WHO collaborating centres… ▪ other ▪ **patient / consumer**

The following recommendation applies:

- To upgrade to E2B(R3), the field value should be copied from the E2B(R2) field into the E2B(R3) field. The effective encoding of the code value should follow the guidance set in the related Implementation Guide.

- To downgrade to E2B(R2), the following cases can occur:

  1) If the field value of E2B(R3) is <u>not</u> 'patient / consumer', the field value should be copied to the field of E2B(R2).

  2) If the field value of E2B(R3) is 'patient / consumer', the field value of E2B(R2) should be set to the code 'other'.

5.2.4 Age Group

E2B(R2) and E2B(R3) expect different codes for the age group:

Description	E2B(R2)		E2B(R3)	
	Field	Code List	Field	Code List
Age group	B.1.2.3	- neonate - infant - child - adolescent - adult - elderly	D.2.3	__foetus__ - neonate - infant - child - adolescent - adult - elderly

The following recommendation applies:

- To upgrade to E2B(R3), the field value should be copied from the E2B(R2) field into the E2B(R3) field. The effective encoding of the code value should follow the guidance set in the Implementation Guide.

- To downgrade to E2B(R2), the following cases can occur:

    1) If the field value of E2B(R3) is <u>not</u> 'foetus', the field value should be copied to the field of E2B(R2).

    2) If the field value of E2B(R3) is 'foetus', no information should be provided in the E2B(R2) field B.1.2.3. Instead, the E2B(R2) field for patient name and initials (i.e., B.1.1 according the E2B(R2) numbering), should be set with the term 'FOETUS'.

5.2.5 Drug Characterization

E2B(R2) and E2B(R3) expect different codes for the characterization of the drug role:

Description	E2B(R2)		E2B(R3)	
	Field	Code List	Field	Code List
Characterization of drug role	B.4.k.1	▪ suspect ▪ concomitant ▪ interacting	G.k.1	▪ suspect ▪ concomitant ▪ interacting ▪ **drug not administered**

The following recommendation applies:

- To upgrade to E2B(R3), the field value should be copied from the E2B(R2) field into the E2B(R3) field.

- To downgrade to E2B(R2), the following cases can occur:

    1) If the field value of E2B(R3) is <u>not</u> set to 'drug not administered', the field value should be copied to the E2B(R2) field.

    2) If the field value of E2B(R3) is set to 'drug not administered', the corresponding E2B(R2) field should be set to 'suspect' and text 'drug not administered' should be appended to the E2B(R2) field on Additional information on drug (i.e., B.4.k.19 according to the E2B(R2) numbering):

        'DRUG NOT ADMINISTERED'

5.2.6 Free Text and Codes for Route of Administration

For the following fields, one guideline expects a code while the other expects a free text value:

Description	E2B(R2)		E2B(R3)	
	Field	Code List	Field	Code List
Route of administration (patient)	B.4.k.8	67 possible codes	G.k.4.r.10.1 G.k.4.r.10.2a G.k.4.r.10.2b	free text Term ID Term ID Version
Route of administration (parent)	B.4.k.9	67 possible codes	G.k.4.r.11.1 G.k.4.r.11.2a G.k.4.r.11.2b	free text Term ID Term ID Version

In E2B(R2), the fields above contain codes as they are defined in the Appendix of the E2B(R2) guideline. In E2B(R3), the same E2B(R2) codes can be used or they can be converted to the codes of EDQM Standard Terms (see USER GUIDE: Use of EDQM terminologies for Dose Forms and Routes of Administration for Individual Case Safety Reports in E2B(R3) message). If standard terms are not available, free text values can be

provided as appropriate free text values. Therefore, the following recommendation applies when E2B(R2) codes are used:

- To upgrade to E2B(R3), there are three possible scenarios:
  1) An E2B(R2) code (i.e., the numeric value) should be copied to the corresponding E2B(R3) code with reference to the E2B(R2) vocabulary:

Example: Input in E2B(R2):   code value: 030

Output in E2B(R3):   Term ID version (field 2a): *E2B / R2*

Term ID (field 2b): 030

  2) If an E2B(R2) RoA term has mapped with an EDQM Standard Term by the EDQM User Guide, the E2B(R2) code (i.e., the numeric value) should be converted to the mapped EDQM RoA Concept Class-Concept Code (i.e., alphabetic numeric value):

Example: Input in E2B(R2):   code value: 030

Output in E2B(R3):   Term ID version (field 2a):
Corresponding Version Number of EDQM RoA Concept Code

Term ID (field 2b): ROA-20035000

  3) If an E2B(R2) RoA term has NOT mapped with an EDQM Standard Term by the EDQM User Guide, the E2B(R2) term should be copied or an appropriate term should be entered in the free text field:

Example: Input in E2B(R2):   code value: 025

Output in E2B(R3):   Free text: Intrahepatic

Term ID version (field 2a): blank

Term ID (field 2b): blank

- To downgrade to E2B(R2), there are three possible scenarios:
  1) If a code is provided in E2B(R3) with reference to the code system / version *E2B / R2*, the code field (i.e., the field 2a) should be copied as is to the E2B(R2) field:

Example: Input in E2B(R3):   Term ID version (field 2a): *E2B / R2*

Term ID (field 2b): 030

Output in E2B(R2):   Code value: 030

2) If a code is provided in E2B(R3) with an EDQM RoA Concept Class-Concept Code (i.e., alphabetic numeric value) and its corresponding term has mapped with an E2B(R2) RoA term, the corresponding E2B(R2) code should be entered in the E2B(R2) field.

Example:	Input in E2B(R3):	Term ID version (field 2a): Corresponding Version Number of EDQM RoA Concept Code
		Term ID (field 2b): ROA-20035000
	Output in E2B(R2):	Code value: 030

3) If a code is provided in E2B(R3) with an EDQM RoA Concept Class-Concept Code (i.e., alphabetic numeric value) and its corresponding term has NOT mapped with an E2B(R2) RoA term, or if a free text field is used in E2B(R3), the code value should be set to '050' (i.e., Other) in the E2B(R2) field, and the information should be copied to the E2B(R2) field B.4.k.19 according to the following examples (with header 'ROUTE' or 'PARENT ROUTE'):

Example 1 (patient route):	Input in E2B(R3):	Term ID version (field 2a): Corresponding Version Number of EDQM RoA Concept Code
		Term ID (field 2b): ROA-20013500
		Or
		Free text: XYZ
	Output in E2B(R2):	Code value: 050
		B.4.k.19 ROUTE: ROA-20013500 (Corresponding Version Number of EDQM RoA Concept Code)
		Or
		B.4.k.19 ROUTE: XYZ

Example 2 (parent route):	Input in E2B(R3):	Term ID version (field 2a): Corresponding Version Number of EDQM RoA Concept Code
		Term ID (field 2b): ROA-20013500
		Or
		Free text: XYZ
	Output in E2B(R2):	Code value: 050

B.4.k.19 PARENT ROUTE: ROA-20013500 (Corresponding Version Number of EDQM RoA Concept Code)

Or

B.4.k.19 PARENT ROUTE: XYZ

Once Term IDs are identified, the recommendations should rely on a mapping between the list of values possible in E2B(R2) and the ones possible in E2B(R3).

5.2.7 Time Interval

E2B(R2) and E2B(R3) expect different codes for the time interval unit:

Description	E2B(R2)		E2B(R3)	
	Field	**Code List**	**Field**	**Code List**
Number of units in interval	B.4.k.5.4	3N	G.k.4.r.2	4N
Time interval unit	B.4.k.5.5	- Year - Month - Week - Day - Hour - Minute	G.k.4.r.3	- UCUM Code {cyclical} {asnecessary} {total}

The following recommendation applies:

- To upgrade to E2B(R3), the field value should be copied from the E2B(R2) field into the E2B(R3) field. The effective encoding of the code value should follow the guidance set in the related Implementation Guide.

- To downgrade to E2B(R2), the following cases can occur:

  1) If the unit value of E2B(R3) is supported in E2B(R2) and if the number of units is not too long, the fields (number and unit) should be copied to the corresponding fields of E2B(R2).

  2) If the number of units is too long (i.e., using 4 digits), the E2B(R2) field should be not provided in field G.k.4.r.2. Instead, the information should be appended to the E2B(R2) field on dosage text (i.e., B.4.k.6), along with the unit:

  Example

    Input in E2B(R3):   number: 0.25 ; unit: h

    Output in E2B(R2):

      B.4.k.6:   Time Interval: \<number\>\<unit\>

3) If the unit value of E2B(R3) is not supported in E2B(R2), the E2B(R2) field should not be provided in field G.k.4.r.2. Instead, the information should be appended to the E2B(R2) field on dosage text (i.e., B.4.k.6):

- When the code is set to 'Cyclical', the dose quantity (value and unit, i.e., G.k.4.r.1a and G.k.4.r.1b) should be copied, followed by the corresponding term :

  <dose-value><dose-unit> CYCLICAL

  <dose-value><dose-unit> AS NECESSARY

  <dose-value><dose-unit> IN TOTAL

4) It should be noted that the conversion of this particular field should be seen in light of the structural changes provided by E2B(R3) on the dosage information (see more information under section 5.7.8).

5) If the field value of E2B(R3) is not present, the field of E2B(R2) should not be provided in the downgraded message.

5.2.8 MedDRA Codes

E2B(R2) and E2B(R3) expect different ways to encode MedDRA codes:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Structured information for disease, surgical procedure…	B.1.7.1a.2	250AN	D.7.1.r.1b	8N
Indication	B.1.8f.2	250AN	D.8.r.6b	8N
Reaction	B.1.8g.2	250AN	D.8.r.7b	8N
Reported cause of death	B.1.9.2.b	250AN	D.9.2.r.1b	8N (*)
Autopsy-determined cause of death	B.1.9.4b	250AN	D.9.4.r.1b	8N (*)
Structured information for disease, surgical procedure…	B.1.10.7.1a.2	250AN	D.10.7.1.r.1b	8N
Indication	B.1.10.8f.2	250AN	D.10.8.r.6b	8N
Reaction	B.1.10.8g.2	250AN	D.10.8.r.7b	8N
Reaction / event in MedDRA terminology	B.2.i.1b	250AN	E.i.2.1b	8N
Test name	B.3.1c	100AN	F.r.2.2b	8N (*)
Sender's diagnosis / syndrome and / or reclassification of reaction / event	B.5.3b	250AN	H.3.r.1b	8N

Although the format defined for MedDRA codes in E2B(R2) is alpha-numeric and composed of 250 characters, the requested information in E2B(R3) is a MedDRA code, composed of 8 digits. Therefore, the following recommendation applies:

- To upgrade to E2B(R3), the following cases can occur:

    1) If the field value of E2B(R2) consists of 8 digits, it should be copied as is to the corresponding E2B(R3) field. For the MedDRA code fields, the corresponding field for the MedDRA version is identical in both messages, and should be copied as is.

    2) If the field value of E2B(R2) does <u>not</u> consist of 8 digits, the field should be ignored unless the E2B(R3) message format foresees a free text field (i.e., see fields flagged with an asterisk). For these fields, the value of E2B(R2) should be copied as is in the free text field of E2B(R3), extended with the MedDRA version field.

        Example: Input in E2B(R2):   code value: free-text

                              Output in E2B(R3):   free text: free-text

- To downgrade to E2B(R2), the MedDRA code value of E2B(R3) should be copied as is into the free text field of E2B(R2). If there is no MedDRA code value, but a free text field,

then the free text field should be copied instead. If both code and free text fields are present, the coded field should be copied along with the MedDRA version field.

5.2.9 Code Lists and UCUM Codes

E2B(R2) and E2B(R3) expect different codes for the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Code List**	**Field**	**Code List**
Age unit (patient)	B.1.2.2b	6 possible codes (incl. decade)	D.2.2b	• UCUM Code • Decade
Gestation period unit (patient)	B.1.2.2.1b	4 possible codes (incl. trimester)	D.2.2.1b	• UCUM Code • Trimester
Age unit (parent)	B.1.10.2.2b	1 possible code	D.10.2.2b	• UCUM Code • Decade
Duration unit	B.2.i.6b	7 possible codes	E.i.6b	• UCUM Code
Dose unit	B.4.k.5.2	32 possible codes	G.k.4.r.1b	• UCUM Code
Cumulative dose unit	B.4.k.5.7	32 possible codes	G.k.5b	• UCUM Code
Duration of drug administration (unit)	B.4.k.15b	6 possible codes	G.k.4.r.6b	• UCUM Code
Gestation period (unit)	B.4.k.10b	4 possible codes (incl. trimester)	G.k.6b	• UCUM Code • Trimester
Time interval (unit)	B.4.k.13.1b B.4.k.13.2b	7 possible codes	G.k.9.i.3.1b G.k.9.i.3.2b	• UCUM Code

The following recommendation applies:

- To upgrade to E2B(R3), the following cases can occur:

    1) If the E2B(R2) unit is 'decade' or 'trimester' (values 800 and 810, respectively), the UCUM unit code should be defined within curly braces.

       Example: Input in E2B(R2):   value 1 ; unit code: 810

       Output in E2B(R3):   value 1 ; unit: {trimester}

    2) In the other case, the corresponding UCUM unit code should be used.

       Example: Input in E2B(R2):   value 10 ; unit code: 003

       Output in E2B(R3):   value 10 ; unit: mg

- To downgrade to E2B(R2), the following cases can occur:

    1) The UCUM unit code used in E2B(R3) should be mapped to a unit of the E2B(R2) guidance. In such case, the corresponding coded value should be copied into the E2B(R2) field. The effective encoding of the unit should follow the guidance set in the related Implementation Guide.

Note that the present specification for backwards and forwards compatibility assumes that the UCUM unit codes used for E2B(R3) messages are the same as the unit codes supported in E2B(R2).

5.2.10 Free Text and UCUM Codes

E2B(R2) and E2B(R3) expect different ways to encode units for:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Code List**
Test unit	B.3.1e	35AN	F.r.3.3	UCUM Code

Although the format defined for the test unit in E2B(R2) is alpha-numeric and composed of 35 characters, it is expected to consist of a UCUM code. Therefore, the following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field should be mapped to the list of UCUM codes, and the mapped code should be copied as is to the E2B(R3) field.
- To downgrade to E2B(R2), the UCUM code value of E2B(R3) should be copied as is into the free text field of E2B(R2).

5.2.11 Re-administration and Recurrence of Reaction on Re-administration

E2B(R2) and E2B(R3) expect different information for the re-administration and the recurrence of reaction on re-administration:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Code List**
Did reaction recur on re-administration?	B.4.k.17.1	▪ Yes ▪ No ▪ Unknown		
Did re-administration take place?			G.k.9.i.4	▪ Re-challenge was done, reaction recurred (yes-yes) ▪ Re-challenge was done, reaction did not recur (yes-no) ▪ Re-challenge was done, outcome unknown (yes) ▪ No re-challenge was done (no)

Only one reaction is a subject for B.4.k.17.1 in E2B(R2) while multiple reactions can be subjects for G.k.9.i.4 in E2B(R3):

- To upgrade to E2B(R3), the following mapping applies, for all the reactions identified to recur within the E2B(R2) field B.4.k.17.2:

    1) If the E2B(R2) value is set to 'Yes', the E2B(R3) value should be set to 'Re-challenge was done, reaction recurred (yes-yes)'.

    2) If the E2B(R2) value is set to 'No', the E2B(R3) value should be set to 'Re-challenge was done, reaction did not recur (yes-no)'.

    3) If the E2B(R2) value is set to 'Unknown', the E2B(R3) value should not beset.

- To downgrade to E2B(R2), the following mapping applies:

    1) If the E2B(R3) value is set to 'Re-challenge was done, reaction recurred (yes-yes)', the E2B(R2) value should be set to 'Yes'.

        - All reactions that recurred on re-administration should be copied in E2B(R2) field B.4.k.17.2 (see section 4.7.11).

    2) If the E2B(R3) value is set to 'Re-challenge was done, reaction did not recur (yes-no)', the E2B(R2) value should be set to 'No'.

    3) If the E2B(R3) value is set to any other value, the E2B(R2) value should be set to 'Unknown'.

5.2.12 Patient and Parent Sex

E2B(R2) and E2B(R3) expect different ways to encode units for:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Code List
Sex (patient)	B.1.5	- Male - Female	D.5	- Male - Female - Null Flavour: UNK, MSK, ASKU, NASK
Sex (parent)	B.1.10.6	- Male - Female	D.10.6	- Male - Female - Null Flavour: UNK, MSK, ASKU, NASK

In both formats, these fields are optional. Therefore, the following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field should be mapped to the list of codes available in E2B(R3). If the field is not set in E2B(R2), the corresponding field should not be set in E2B(R3).

- To downgrade to E2B(R2), the E2B(R3) field should be mapped to the list of codes available in E2B(R2). If the field is not set in E2B(R3), or if the field is set to 'Unknown', or if the field is attached to a null flavour, the corresponding field should not be set in E2B(R2).

5.2.13 Acknowledgement Codes

E2B(R2) and E2B(R3) expect different ways to encode codes for:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Code List**
ACK Transmission code	ACK: A.1.6	▪ 01 (All Reports loaded into database) ▪ 02 (ICSR Error, not all reports loaded into the database) ▪ 03 (SGML parsing error, no data extracted)	ACK: ACK.A.4	▪ AA (Application Acknowledgement Accept) ▪ AE (Application Acknowledgment Error) ▪ <u>AR (Application Acknowledgment Reject)</u>
ACK Code for report	ACK: B.1.8	▪ 01 (Report loaded successfully) ▪ 02 (Report not loaded)	ACK: ACK.B.r.6	▪ <u>CA (Commit Accept)</u> ▪ <u>CR (Commit Reject)</u>

The following recommendation applies:

- To upgrade to E2B(R3), the field A.1.6 of the E2B(R2) ACK should be mapped as follows:
    1) E2B(R2) code '01'should be converted to E2B(R3) code 'AA'.
    2) E2B(R2) code '02'should be converted to E2B(R3) code 'AE'.
    3) E2B(R2) code '03'should be converted to E2B(R3) code 'AR'.

- To upgrade to E2B(R3), the field B.1.8 of the E2B(R2) ACK should be mapped as follows:
    1) E2B(R2) code '01'should be converted to E2B(R3) code 'CA'.
    2) E2B(R2) code '02'should be converted to E2B(R3) code 'CR'.

- To downgrade to E2B(R2), the E2B(R3) field should be mapped as follows:
    1) E2B(R3) code 'AA' should be converted to E2B(R2) code '01'.
    2) E2B(R3) code 'AE' should be converted to E2B(R2) code '02'.
    3) E2B(R3) code 'AR' should be converted to E2B(R2) code '03'.
    4) E2B(R3) code 'CA' should be converted to E2B(R2) code '01'.
    5) E2B(R3) code 'CR' should be converted to E2B(R2) code '02'.

5.3 Deletion

Some fields of E2B(R2) have been deleted in E2B(R3). Guidance is provided on the way to handle such fields.

5.3.1 Fields to Ignore

The following fields have been deleted in E2B(R3) as they are no longer useful anymore for handling case safety reports:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Was the case medically confirmed?	A.1.14	1N	-	-
MedDRA version for reaction / event term PT	B.2.i.2	8AN / 250AN	-	-
ACK Safety report version	ACK: B.1.2	2AN	-	-
ACK Authority number ACK Company number	ACK: B.1.4 ACK: B.1.5	100AN 100AN	-	-
ACK Date of receipt of the most recent information	ACK: B.1.7b	8N	-	-

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field should be ignored as there is no counterpart element in E2B(R3).

- To downgrade to E2B(R2), the field should not be provided in E2B(R2), as the related field is optional in E2B(R2).

5.3.2 Fields with Default Value

The following fields have been deleted in E2B(R3) but should receive a default value when converted back to E2B(R2), as they are required in E2B(R2):

Description	E2B(R2)		E2B(R3)	
	Field	Default Value	Field	Format
ACK: Message type	ACK: M.1.1	ichicsrack	-	-
Message format version	(ACK) M.1.2	2.1	-	-
Message format release	(ACK) M.1.3	1.0	-	-
Information on receiver of case safety report	A.3.2	*empty root element*	-	-

The following recommendation applies:

- To upgrade to E2B(R3), the fields of E2B(R2) should be ignored, as there is no counterpart element in E2B(R3).

- To downgrade to E2B(R2), the following cases occur:

  1) Field M.1.1 should receive the default value 'ichicsrack' (in ICSR ACK).

  2) Field M.1.2 should receive the default value '2.1' (in ICSR and ICSR ACK).

  3) Field M.1.3 should receive the default value '1.0' (in ICSR and ICSR ACK).

  4) Field A.3.2 should be created with the empty root element 'receiver'.

5.3.3 Safety Report Version Number

This E2B(R2) field does not exist in E2B(R3) but the related treatment is covered in section 5.1.4.

5.3.4 Number of Separate Dosages

E2B(R3) has reviewed the structure of information regarding dosage, and the field related to the number of separate dosages (i.e., B.4.k.5.3 according to the E2B(R2) field numbering) has been deleted.

The recommendations regarding this element should be retrieved from the section dedicated to the dosage information, section 5.7.8.

5.4 Addition

Some fields have been added in E2B(R3). Guidance is provided on the way to handle such fields, depending on whether the E2B(R3) field has a counterpart in E2B(R2), or whether some mapping can be defined.

5.4.1 Fields with No Mapping

The following fields have been added in E2B(R3), with no counterpart in E2B(R2):

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Included documents (held by the sender)	-	-	C.1.6.1.r.2	File
Primary source telephone	-	-	C.2.r.2.7	33AN
Included documents (literature references)	-	-	C.4.r.2	File
Family history (patient)	-	-	D.7.1.r.6	Boolean
Concomitant therapies	-	-	D.7.3	Boolean
Medical confirmation by health professional	-	-	E.i.8	Boolean
MedDRA code for Test Name			F.r.2.2b	8N

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R3) field should not be provided, as there is no counterpart element in the E2B(R2) guideline.

- To downgrade to E2B(R2), the value of the E2B(R3) field should be captured in narrative field (B.5.1).

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
ACK Date of transmission	-	-	ACK: ACK.B.r.5	Date

- To upgrade to E2B(R3), the E2B(R3) field should not be provided, as there is no counterpart element in the E2B(R2) guideline.

- To downgrade to E2B(R2), ACK.B.r.5 field should be blank.

5.4.2 Study Registration

In E2B(R3), the study registration number and the study registration country have been added:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Study registration number	-	-	C.5.1.r.1	50AN ASKU, NASK
Study registration country	-	-	C.5.1.r.2	2A ASKU, NASK

The following recommendation applies:

- To upgrade to E2B(R3), these two fields should not be provided, as there is no counterpart in the E2B(R2) guideline, and therefore no value in the E2B(R2) message.

- To downgrade to E2B(R2), the study registration number(s) and country(ies) should be copied to the E2B(R2) message as a prefix for the study name field, i.e., A.2.3.1 according to the E2B(R2) field numbering. The study registration number can repeat in E2B(R3), and when copied back into E2B(R2), repeated fields should appear separated by a comma. If one of these fields is nullified, the term 'UNKNOWN' should be used instead.

 Example: Input in E2B(R3):

   Study #1: registration number(s): 111 for UK, 222 for BE

   Study #2: registration number(s): 333 for FR, ASKU for IT

  Output in E2B(R2): study name:

   Study #1: 111 (UK),222 (BE):<study-name-1>

   Study #2: 333 (FR), UNKNOWN (IT): <study-name-2>

5.4.3 ISO IDMP identifiers

M5 identifiers have been renamed to ISO IDMP terms and identifiers. E2B(R3) supports the concepts of MPID and PhPID for the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
MPID and MPID version for patient drug history	-	-	D.8.r.2a D.8.r.2b	AN AN
PhPID and PhPID version for patient drug history	-	-	D.8.r.3a D.8.r.3b	AN AN
MPID and MPID version for parent drug history	-	-	D.10.8.r.2a D.10.8.r.2b	AN AN
PhPID and PhPID version for parent drug history	-	-	D.10.8.r.3a D.10.8.r.3b	AN AN
MPID and MPID version for drug identification	-	-	G.k.2.1.1a G.k.2.1.1b	AN AN
PhPID and PhPID version for drug identification	-	-	G.k.2.1.2a G.k.2.1.2b	AN AN
Substance TermID and version	-	-	G.k.2.3.r.2a G.k.2.3.r.2b	AN AN
Dose Form TermID and version			G.k.4.r.9.2a G.k.4.r.9.2b	AN AN

The following recommendation applies:

- To upgrade to E2B(R3), the field should not be provided, as there is no counterpart to this field in the E2B(R2) guideline.

- To downgrade to E2B(R2), the drug identification should be copied to the E2B(R2) message as a prefix for the related drug name field (see the mapping below). For each drug, the following fields should be copied: MPID and MPID version date / number, or PhPID and PhPID version date / number. Information should be preceded by the prefix 'MPID' or 'PhPID'. The version dates should display between parentheses. MPID or PhPID and the drug name should repeat, if appropriate, separated by a semi-colon.

  The correspondence between the identification and name fields is as follows:

  1) D.8.r.2a-2b-3a-3b should be copied as prefix of the field B.1.8aof E2B(R2).

  2) D.10.8.r.2a-2b-3a-3b should be copied as prefix of the field B.1.10.8a of E2B(R2).

  3) G.k.2.1.1a-1b-2a-2b should be copied as prefix of the field B.4.k.2.1 of E2B(R2).

  Example: Input in E2B(R3):

  MPID: abcdef ; version date / number: 20080925

  or   PhPID: ghijkl ; version date / number: 20081028

Output in E2B(R2):

    MPID: abcdef (20080925): <drug name>

or   PhPID: ghijkl (20081028): <drug name>

5.4.4 Investigational Product Blinded

E2B(R3) supports the concepts of investigational product blinded:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Investigational product blinded	-	-	G.k.2.5	Boolean

The following recommendation applies:

- To upgrade to E2B(R3), the field should not be set.

- To downgrade to E2B(R2), if the field is set to 'true', the term 'INVESTIGATIONAL' should be added to the E2B(R2) field B.4.k.19 (additional information on the drug).

5.4.5 Case Narrative in Native Language

The case narrative field in native language has been added in E2B(R3):

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Case summary and reporter's comment text / language	-	-	H.5.r.1a H.5.r.1b	100000 AN 3A

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R3) field should not be provided, as there is no counterpart element in the E2B(R2) guideline.

- To downgrade to E2B(R2), the fields H.5.r.1a and H.5.r.1b of E2B(R3) should be appended to the case narrative section, i.e., B.5.1 of E2B(R2). The information should be preceded by the prefix 'CASE SUMMARY', extended with the identification of the language between parentheses.

Example: Input in E2B(R3):

Reporter's comments text: abcdefghikjkl

Reporter's comments language: jap

Output in E2B(R2):

<content of case narrative>

CASE SUMMARY (jap): abcdefghikjkl

5.4.6 Reaction as Reported and Translated

The following field has been added in E2B(R3), with no counterpart in E2B(R2):

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Reaction / event as reported by primary source	B.2.i.0	200AN	E.i.1.1a	250AN
Reaction / event as reported by primary source (translation)	-	-	E.i.1.2	250AN

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R3) field should not be provided, as there is no counterpart element in the E2B(R2) guideline.

- To downgrade to E2B(R2), the following cases occur:

    1) If the E2B(R3) field E.i.1.2 is set, it should be copied into the E2B(R2) field B.2.i.0, truncated if appropriate, as described in section 5.5.2.

    2) If the E2B(R3) field E.i.1.2 is not set, the E2B(R3) field E.i.1.1a should be copied with the E2B(R3) field E.i.1.1b (language code) into the E2B(R2) field B.2.i.0, truncated if appropriate, as described in section 5.5.2.

5.4.7 Reported cause(s) of death

The following field in E2B(R2) is split into two field in E2B(R3):

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Reported cause(s) of death	B.1.9.2b	250AN	D.9.2.r.1b	8N
Reported Cause(s) of Death (Free text)	-	-	D.9.2.r.2	250AN

The E2B(R2) Guideline recommends 'MedDRA if applicable' for this data element, the following recommendation applies:

- To upgrade to E2B(R3):

    1) Populate E2B(R3) D.9.2.r.1b field with E2B(R2) B.1.9.2b data if MedDRA code is used in the report.

    2) Populate E2B(R3) D.9.2.r.2 field with E2B(R2) B.1.9.2b data if it is free text in the report.

- To downgrade to E2B(R2), the following cases occur:

    1) If only the E2B(R3) D.9.2.r.1bfield is set, it should be copied into the E2B(R2) field B.1.9.2b.

    2) If only the E2B(R3) D.9.2.r.2 field is set, it should be copied into the E2B(R2) field B.1.9.2b.

    3) If both E2B(R3) D.9.2.r.1b and E2B(R3) D.9.2.r.2 fields are set:

        - Copy only the E2B(R3) D.9.2.r.1b field into the E2B(R2) field B.1.9.2b.

        - Copy the E2B(R3) B.1.9.2.r.b2 field into narrative field.

5.4.8 Autopsy-determined Cause(s) of Death

The following field in E2B(R2) is split into two field in E2B(R3):

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Autopsy-determined Cause(s) of Death	B.1.9.4b	250AN	D.9.4.r.1b	8N
Autopsy-determined Cause(s) of Death (Free text)	-	-	D.9.4.r.2	250AN

The E2B(R2) Guideline recommends 'MedDRA if applicable' for this data element, the following recommendation applies:

- To upgrade to E2B(R3):

    1) Populate E2B(R3) D.9.4.r.1b field with E2B(R2) B.1.9.4.b data if MedDRA code is used in the report.

    2) Populate E2B(R3) D.9.4.r.2 field with E2B(R2) B.1.9.4b data if it is free text in the report.

- To downgrade to E2B(R2), the following cases occur:

    1) If only the E2B(R3) D.9.4.r.1b field is set, it should be copied into the E2B(R2) field B.1.9.4b.

2) If only the E2B(R3) D.9.4.r.2 field is set, it should be copied into the E2B(R2) field B.1.9.4b.

3) If both E2B(R3) D.9.4.r.1b and E2B(R3) D.9.4.r.2 fields are set:

   ▪ Copy only the E2B(R3) D.9.4.r.1b field into the E2B(R2) field B.1.9.4b.

   ▪ Copy the E2B(R3) B.1.9.4.r.b2 field into narrative field.

5.5 Field Length

For some fields, the length has been extended in E2B(R3). Guidance is provided on the conversion of such fields, depending on whether truncation is appropriate or not.

5.5.1 Extended Fields to Truncate

The following fields have been extended in E2B(R3), and the effective size can be found in the Implementation Guide of E2B(R3). These fields should be truncated when converted back to E2B(R2):

Description	E2B(R2)		E2B(R3)	
	Field	Field Size	Field	Field Size
Reporter given name, middle name and family name	A.2.1.1b	35	C.2.r.1.2	60 (*)
	A.2.1.1c	15	C.2.r.1.3	60 (*)
	A.2.1.1d	50	C.2.r.1.4	60 (*)
Sender organization	A.3.1.2	60	C.3.2	100
Sender title, given name, middle name and family name	A.3.1.3b	10	C.3.3.2	50
	A.3.1.3c	35	C.3.3.3	60
	A.3.1.3d	15	C.3.3.4	60
	A.3.1.3e	35	C.3.3.5	60
Patient / parent initials	B.1.1	10	D.1	60 (*)
	B.1.10.1	10	D.10.1	60 (*)
Test name (free text)	B.3.1c	100	F.r.2.1	250
Dosage text	B.4.k.6	100	G.k.4.r.8	2000
Pharmaceutical dose form text	B.4.k.7	50	G.k.4.r.9.1	60 (*)
Method and result of assessment	B.4.k.18.3	35	G.k.9.i.2.r.2	60
	B.4.k.18.4	35	G.k.9.i.2.r.3	60

The following recommendation applies:

• To upgrade to E2B(R3), the E2B(R2) field should be copied into the field of E2B(R3).

• To downgrade to E2B(R2), the following cases occur:

   1) If the field value does not exceed the size limitation set by the E2B(R2) guideline, the field value should be copied to the element of E2B(R2).

2) If the field value exceeds the size limitation set by the E2B(R2) guideline, the field value should be truncated to the size limitation set by the E2B(R2) guideline, less 3 characters, which are replaced by '…' so as to highlight that truncation has been applied.

Example: Input in E2B(R3):

Field with size of 20 characters: 123456789012345

Output in E2B(R2):

Field with size of 10 characters: 1234567…

Fields with an asterisk (*) can be masked (for privacy or because information is unknown). The conversion of such fields is described in section 5.6.

5.5.2 Extended Fields to Keep

The following fields have been extended in E2B(R3), and the effective size can be found in the Implementation Guide of E2B(R3). These fields should be truncated when converted back to E2B(R2), but the full value should be copied to the narrative section of E2B(R2):

Description	E2B(R2)		E2B(R3)	
	Field	Field Size	Field	Field Size
List of documents held by the sender	A.1.8.2	100	C.1.6.1.r.1	2000
Source of the case identifier	A.1.11.1	50	C.1.9.1.r.1	100
Reason for Nullification / Amendment	A.1.13.1	200	C.1.11.2	2000
Study name Sponsor study name	A.2.3.1 A.2.3.2	100 35	C.5.2 C.5.3	2000 50
Medical history (patient and parent)	B.1.7.1g B.1.10.7.1g	100	D.7.1.r.5 D.10.7.1.r.5	2000
Name of the drug as reported (patient and parent)	B.1.8a B.1.10.8a	100 100	D.8.r.1 D.10.8.r.1	250 250
Reaction / event as reported by the primary source	B.2.i.0	200	E.i.1.1a	250
Medicinal product as reported by primary source	B.4.k.2.1	70	G.k.2.2	250
Substance name	B.4.k.2.2	100	G.k.2.3.r.1	250
Additional information on drug (free text)	B.4.k.19	100	G.k.11	2000
Reporter's comments	B.5.2	500	H.2	20000
Sender's Comments	B.5.4	2000	H.4	20000

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2)field should be copied into the field of E2B(R3).

- To downgrade to E2B(R2), the following cases occur:
    1) If the field value does not exceed the size limitation set by the E2B(R2) guideline, the field value should be copied to the element of E2B(R2).
    2) If the field value exceeds the size limitation set by the E2B(R2) guideline, the field value should be truncated to the size limitation set by the E2B(R2) guideline, less 3 characters, which are replaced by '…' so as to highlight that truncation has been applied. In addition, the field of E2B(R3) should be completely copied into the narrative section of E2B(R2), i.e., B.5.1 of E2B(R2). The information should be preceded by a prefix depending on the field to be copied:

▪ A.1.8.2 / C.1.6.1.r.1	ADDITIONAL DOCUMENTS
▪ A.1.11.1 / C.1.9.1.r.1	CASE IDENTIFIER
▪ A.1.13.1 / C.1.11.2	NULLIFICATION / AMENDMENT REASON
▪ A.2.3.1 / C.5.2	STUDY NAME
▪ A.2.3.2 / C.5.3	SPONSOR STUDY NUMBER
▪ B.1.7.1g / D.7.1.r.5	MEDICAL HISTORY
▪ B.1.8a / D.8.r.1	DRUG HISTORY
▪ B.1.10.7.1g / D.10.7.1.r.5	PARENT MEDICAL HISTORY
▪ B.1.10.8a / D.10.8.r.1	PARENT DRUG HISTORY
▪ B.2.i.0 / E.i.1.1a	REACTION / EVENT
▪ B.4.k.2.1 / G.k.2.2	DRUG
▪ B.4.k.2.2 / G.k.2.3.r.1	ACTIVE INGREDIENT
▪ B.4.k.19 / G.k.11	ADDITIONAL INFORMATION ON DRUG
▪ B.5.2 / H.2	REPORTER COMMENTS
▪ B.5.4 / H.4	SENDER COMMENTS

Example: Input in E2B(R3):   Field with size of 120 characters: 123456789012345

Output in E2B(R2):   Field with size of 100 characters: 1234567…

Case narrative section (for the study name part):

<case narrative section>

STUDY NAME: 123456789012345

5.5.3 Length of Numeric Fields (Extended)

The size of the following numeric field has been extended in E2B(R3):

Description	E2B(R2)		E2B(R3)	
	Field	**Field Size**	**Field**	**Field Size**
Age (parent)	B.1.10.2.2a	2	D.10.2.2a	3

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field should be copied into the field of E2B(R3).

- To downgrade to E2B(R2), the following cases occur:

  1) If 2 digits are used, the field of E2B(R3) should be copied into the field of E2B(R2).

  2) If 3 digits are used, the field of E2B(R2) should be set to '99'.

5.6 Null Flavour

For several fields, E2B(R3) provides null flavoured information, for privacy purposes or because information is unknown. Guidance is provided on the way to pass from one encoding to the other, and vice versa.

5.6.1 Null Flavour for Optional Free Text Fields

In E2B(R3), the following optional text fields can be encoded with a null flavour:

Description	E2B(R2)		E2B(R3)	
	Field	**Supported Masks**	**Field**	**Supported Masks**
Reporter's title	A.2.1.1a	-	C.2.r.1.1	MSK, ASKU, NASK, UNK
Reporter's given, middle and family name	A.2.1.1b A.2.1.1c A.2.1.1d	-	C.2.r.1.2 C.2.r.1.3 C.2.r.1.4	MSK, ASKU, NASK
Reporter's organization and department	A.2.1.2a A.2.1.2b	-	C.2.r.2.1 C.2.r.2.2	MSK, ASKU, NASK
Reporter's street, city, state or province and post code	A.2.1.2c A.2.1.2d A.2.1.2e A.2.1.2f	-	C.2.r.2.3 C.2.r.2.4 C.2.r.2.5 C.2.r.2.6	MSK, ASKU, NASK

The following recommendation applies:

- To upgrade to E2B(R3), the following cases occur:

  1) If the E2B(R2) field is not set, the E2B(R3) field should not be provided (as it is optional).

2) If the E2B(R2) field is set to 'UNKNOWN'

- If supported, the E2B(R3) field should be provided with the unknown null flavour (UNK).

- If not supported, the E2B(R3) field should not be provided.

3) If the E2B(R2) field is set to 'PRIVACY'

- If supported, the E2B(R3) field should be provided with the mask null flavour (MSK).

- If not supported, the E2B(R3) field should not be provided.

4) In any other case, the field should be copied according to recommendations defined in the other sections of this document, if applicable.

- To downgrade to E2B(R2), the E2B(R3) field should be copied into the field of E2B(R2).

1) If the E2B(R3) field is not set, the E2B(R2) field should not be provided (as it is optional).

2) If the E2B(R3) field is provided with an unknown null flavour (UNK, ASKU, NASK), the E2B(R2) field should be provided with the default term 'UNKNOWN'.

3) If the E2B(R3) field is provided with the mask null flavour (MSK), the E2B(R2) field should be provided with the default term 'PRIVACY'.

4) In any other case, the field should be copied according to recommendations defined in the other sections of this document, if applicable.

The other E2B(R3) fields that can receive a null flavour (UNK, ASKU, NASK, NI, MSK…) should be ignored when converted back to E2B(R2), i.e., the related E2B(R2) field should not be set.

5.6.2 Null Flavour for Fields Required in E2B(R3)

In E2B(R3), the following required fields can be encoded with a null flavour:

Description	E2B(R2)		E2B(R3)	
	Field	Supported Masks	Field	Supported Masks
Patient (name or initials)	B.1.1	-	D.1	MSK, ASKU, NASK, UNK

The following recommendation applies:

- To upgrade to E2B(R3), the following cases occur:

1) If the E2B(R2) field is not provided, the corresponding E2B(R3) field should be provided with the null flavour set to 'unknown' (UNK).

2) If the E2B(R2) field 'Initials' (i.e., B.1.1) is provided with the value 'UNKNOWN', the corresponding E2B(R3) field should be provided with the null flavour set to 'unknown' (UNK).

3) If the E2B(R2) field 'Initials' (i.e., B.1.1) is provided with the value 'PRIVACY', the corresponding E2B(R3) field should be provided with the null flavour set to 'mask' (MSK).

- To downgrade to E2B(R2), the following cases occur:

    1) If the E2B(R3) field 'Initials' (i.e., D.1) is provided with the null flavour set to 'unknown' (UNK, NASK or ASKU), the corresponding E2B(R2) field should be provided with the default value 'UNKNOWN'.

    2) If the E2B(R3) field 'Initials' (i.e., D.1) is provided with the null flavour set to 'mask' (MSK), the corresponding E2B(R2) field should be provided with the default value 'PRIVACY'.

5.6.3 Null Flavour for Optional Codes and Dates

In E2B(R3), the following code and date fields can be encoded with a null flavour:

Description	E2B(R2)		E2B(R3)	
	Field	Supported Masks	Field	Supported Masks
Reporter's country code	A.2.1.3	-	C.2.r.3	MSK, ASKU, NASK, UNK
Qualification	A.2.1.4	-	C.2.r.4	UNK
Date of birth (patient)	B.1.2.1b	-	D.2.1	MSK
Was Autopsy Done?	B.1.9.3	3=Unknown	D.9.3	ASKU, NASK,UNK
Date of birth (parent)	B.1.10.2.1b	-	D.10.2.1	MSK, ASKU, NASK
Continuing (patient or parent medical history)	B.1.7.1d B.1.10.7.1d	3=Unknown	D.7.1.r.3 D.10.7.1.r.3	MSK, ASKU, NASK, UNK

The following recommendation applies:

- To upgrade to E2B(R3), the following cases occur:

    1) If the field 'Was Autopsy Done' (i.e., B.1.9.3) or 'Continuing (patient or parent medical history)' (i.e., B.1.7.1d or B.1.10.7.1d) is provided with value '3' (unknown) in E2B(R2), the corresponding field should be provided in E2B(R3) with the null flavour (UNK).

2) If any of the other fields are not provided in E2B(R2), the corresponding fields in E2B(R3) should not be provided.

- To downgrade to E2B(R2), the following cases occur:

    1) If the field 'Was Autopsy Done' (i.e., D.9.3) or 'Continuing (patient or parent medical history)' (i.e., D.7.1.r.3 or D.10.7.1.r.3) has null flavour (UNK) in E2B(R3), the corresponding field in E2B(R2) should be provided with value '3' (unknown).

    2) If any of the other fields has a null flavour in E2B(R3), the corresponding field in E2B(R2) should not be provided.

5.7 Structure

For several fields, E2B(R3) provides a new way to structure the information on case safety reports. Guidance is provided on the way to pass from one structure to the other, and vice versa.

5.7.1 Country of Primary Source

In E2B(R3), the primary source entity can repeat, with one primary source selected for regulatory purposes. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Identification of the country of the primary source	A.1.1	2A	-	-
Reporter country code	A.2.1.3	2A	C.2.r.3	2A
Primary source for regulatory purposes	-	-	C.2.r.5	1N

The following recommendation applies:

- To upgrade to E2B(R3):

    1) The E2B(R2) field A.1.1 should be ignored.

    2) Each E2B(R2) entity A.2.1 (Primary Source) should be mapped to an entity C.2.r.1 in E2B(R3).

    3) For each Primary Source, the E2B(R2) field A.2.1.3 should be copied to the E2B(R3) field C.2.r.3.

    4) The field C.2.r.5 of E2B(R3) should be set to '1' for the first occurrence of the Primary Source available in the E2B(R2) message. The other Primary Source occurrences should not have the field C.2.r.5set.

- To downgrade to E2B(R2):

1) The E2B(R2) field A.1.1 should be filled with the country value (i.e., the E2B(R3) field C.2.r.3) of the Primary Source that was set for regulatory purposes (i.e., with E2B(R3) field C.2.r.5 set to '1').

2) Each E2B(R3) entity C.2.r.1 (Primary Source) should be mapped to an entity A.2.1 in E2B(R2).

3) For each Primary Source, the E2B(R3) field C.2.r.3 should be copied to the E2B(R2) field A.2.1.3.

4) The field C.2.r.5 of E2B(R3) should be ignored.

5.7.2 Country of Reaction / Event

E2B(R3) provides a different approach for the country of reaction / event, as it is stored at the level of the case, i.e., unique, in E2B(R2) and at the level of the reaction, i.e., repeatable, in E2B(R3). The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Country where the reaction / event occurred	A.1.2 *unique*	2A	-	-
Country where the reaction / event occurred	-	-	E.i.9 *repeatable*	2A

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field A.1.2 should be copied into all the occurrences of the E2B(R3) field E.i.9, i.e., with the same value for all the reactions / events.

- To downgrade to E2B(R2), the E2B(R3) field E.i.9 of the first occurrence of the reaction / event having a E.i.9 field set, should be copied into the E2B(R2) field A.1.2, i.e., at the case report level. The other country fields in the reaction / event section should be ignored.

5.7.3 Unique Case Number

E2B(R3) provides a different approach for the unique case number. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Regulatory authority's case report number	A.1.10.1	100AN	-	-
Worldwide unique case identifier	-	-	C.1.8.1	100AN
Other sender's case report number	A.1.10.2	100AN	-	-
First sender of this case	-	-	C.1.8.2	▪ regulator ▪ other

The following recommendation applies:

- To upgrade to E2B(R3), the following cases can occur:

    1) If the E2B(R2) field A.1.10.1 for the regulatory authority's number is provided, the field value should be copied into the E2B(R3) field C.1.8.1, and field C.1.8.2 should be set to 'regulator'.

    2) If the E2B(R2) field A.1.10.2 for the other sender's number is provided, the field value should be copied into the E2B(R3) field C.1.8.1, and field C.1.8.2 should be set to 'other'.

    3) If both fields are provided in the E2B(R2) message, only the regulatory authority's number should be converted.

- To downgrade to E2B(R2), the following cases can occur:

    1) If the E2B(R3) field C.1.8.2 is set to 'regulator', the E2B(R3) field C.1.8.1 should be copied into the E2B(R2) field A.1.10.1 (i.e., regulatory authority's number).

    2) If the E2B(R3) field C.1.8.2 is set to 'other', the E2B(R3) field C.1.8.1 should be copied into the E2B(R2) field A.1.10.2 (i.e., other sender's number).

5.7.4 Sender's Telephone and Fax

E2B(R3) provides a different approach for the sender's telephone and fax. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Sender's telephone	A.3.1.4f	10AN	C.3.4.6	33AN
Sender's telephone extension	A.3.1.4g	5AN	-	-
Sender's telephone country code	A.3.1.4h	3AN	-	-
Sender's fax	A.3.1.4i	10AN	C.3.4.7	33AN
Sender's fax extension	A.3.1.4j	5AN	-	-
Sender's fax country code	A.3.1.4k	3AN	-	-

The following recommendation applies:

- To upgrade to E2B(R3), the three E2B(R2) fields should be merged, along with the prefix 'tel' or 'fax', and copied into the single E2B(R3) field. There is no limitation in the field size.

  Example: Input in E2B(R2):

                    phone: 12345678

                    phone extension: 123

                    phone country code: +44

            Output in E2B(R3):

                    phone: tel: +44 12345678 123

- To downgrade to E2B(R2), the single E2B(R3) field should be copied, without the prefix 'tel' or 'fax', into the corresponding E2B(R2) field (i.e., the longest field). If the value to be copied is too long, the value should be truncated.

  Example 1:   Input in E2B(R3):

                    phone: tel: +44 123456

            Output in E2B(R2):

                    phone: +44 123456

  Example 2:   Input in E2B(R3):

                    phone: tel: +44 12345678 123

            Output in E2B(R2):

                    phone: +44 123…

5.7.5 Literature References

E2B(R3) provides a different approach for the literature references. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Literature references	A.2.2 *in primary source*	500AN	C.4.r.1 *in safety report*	500AN ASKU, NASK

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field A.2.2 from all the primary sources should be copied, and these values should be copied into E2B(R3) field C.4.r.1 so as to have one entry per primary source.

- To downgrade to E2B(R2), all the not-nullified E2B(R3) fields C.4.r.1 should be copied, and these values should be copied into the E2B(R2) field A.2.2 of the primary source for regulatory purposes. Fields should be separated with a semi-colon. If the value to be copied extends the field size limit, the information should be truncated.

5.7.6 Seriousness and Seriousness Criteria

E2B(R3) provides a different approach for the seriousness criteria. In E2B(R3), such information is stored in the reaction / event section, and could therefore be provided for each reaction / event. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Seriousness	A.1.5.1 *report level*	▪ Yes ▪ No	-	-
Seriousness criteria (*6 different criteria*)	A.1.5.2 *report level*	▪ Yes ▪ No	E.i.3.2 *reaction level*	▪ true ▪ Null Flavour (NI)
Term highlighted by the reporter	B.2.i.3 *reaction level*	▪ yes, highlighted by the reporter, NOT serious ▪ no, not highlighted by the reporter, NOT serious ▪ yes, highlighted by the reporter, SERIOUS ▪ no, not highlighted by the reporter, SERIOUS	E.i.3.1 *reaction level*	▪ Yes, highlighted by the reporter, NOT serious ▪ No, not highlighted by the reporter, NOT serious ▪ Yes, highlighted by the reporter, SERIOUS ▪ No, not highlighted by the reporter, SERIOUS

The following recommendation applies:

- To upgrade to E2B(R3):

  1) The E2B(R2) field B.2.i.3 (term highlighted by the reporter) should be mapped to the E2B(R3) field E.i.3.1 (same values).

  2) The E2B(R2) fields for seriousness criteria, stored at the safety report level, i.e., A.1.5.2, should be copied to the E2B(R3) field E.i.3.2 of each reaction / event if the E2B(R2) field B.2.i.3 is set to 'serious'. The E2B(R3) field E.i.3.2 should be set to 'NI' for each reaction / event if the E2B(R2) field B.2.i.3 is set to 'not serious'.

  3) The E2B(R2) fields for seriousness criteria, stored at the safety report level, i.e., A.1.5.2 should be copied to the E2B(R3) field E.i.3.2 of each reaction / event if the E2B(R2) field B.2.i.3 is not provided.

  4) Example 1:

     Input in E2B(R2):

       Seriousness criteria (A.1.5.2): death: yes; disabling: no

       Reaction 1 (B.2.i.3): yes, highlighted, serious

       Reaction 2 (B.2.i.3): no, not highlighted, not serious

     Output in E2B(R3):

       Reaction 1:

         Term highlighted by reporter (E.i.3.1): yes, highlighted, serious

         Seriousness criteria (E.i.3.2): death: true; life threatening: NI;

         Hospitalisation: NI; disabling: NI; Birth defect: NI; Other: NI

       Reaction 2:

         Term highlighted by reporter (E.i.3.1): no, not highlighted, not serious

         Seriousness criteria (E.i.3.2): death: NI; life threatening: NI;

          Hospitalisation: NI; disabling: NI; Birth defect: NI; Other: NI

     Example 2:

     Input in E2B(R2):

       Seriousness criteria (A.1.5.2): death: yes; disabling: no

       Reaction 1 (B.2.i.3): yes, highlighted, serious

       Reaction 2 (B.2.i.3): blank

     Output in E2B(R3):

Reaction 1:

Term highlighted by reporter (E.i.3.1): yes, highlighted, serious

Seriousness criteria (E.i.3.2): death: yes; life threatening: NI;

Hospitalisation: NI; disabling: NI; Birth defect: NI; Other: NI

Reaction 2:

Term highlighted by reporter (E.i.3.1): blank

Seriousness criteria (E.i.3.2): death: yes; life threatening: NI;

Hospitalisation: NI; disabling: NI; Birth defect: NI; Other: NI

- To downgrade to E2B(R2):

  1) The E2B(R3) field E.i.3.1 (term highlighted by the reporter) should be mapped to the E2B(R2) field B.2.i.3 (same values).

  2) The E2B(R2) field A.1.5.1 should be set to 'Yes' if there is at least one reaction / event with the corresponding seriousness criteria set to 'true' (i.e., E2B(R3) field E.i.3.2).

  3) Each seriousness criteria (i.e., E2B(R2) fields A.1.5.2) should be set to 'Yes' if there is at least one reaction / event, highlighted as serious, with the corresponding criteria set to 'true' (i.e., E2B(R3) field E.i.3.2).

  Example:

  Input in E2B(R3):

  Reaction 1:

  Term highlighted by reporter (E.i.3.1): yes, serious

  Seriousness criteria (E.i.3.2): death: yes; disabling: no

  Reaction 2:

  Term highlighted by reporter (E.i.3.1): no, serious

  Seriousness criteria (E.i.3.2): death: no; disabling: yes

  Output in E2B(R2):

  Serious (A.1.5.1): yes

  Seriousness criteria (A.1.5.2): death: yes; disabling: yes

  Reaction 1 (B.2.i.3): Yes, highlighted, serious

  Reaction 2 (B.2.i.3): No, not highlighted, serious

5.7.7 Results of Tests

E2B(R3) provides a different approach for the results of tests. In E2B(R3), the test result can be expressed as a value, with or without a qualifier, or coded. Additionally, the E2B(R3) field on the results can repeat for each test. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Test result	B.3.1d	50AN	F.r.3.1 F.r.3.2 F.r.3.4	as code (1N) as value (50N) free text (2000AN)
Results of tests	B.3.2 *unique*	2000AN	F.r.3.4	2000AN

The following recommendation applies:

- To upgrade to E2B(R3), the following recommendations apply:

  1) The upgrade of the E2B(R2) field B.3.1.d depends on its content:

     - If the E2B(R2) field B.3.1.d is numeric, the content should be copied as is to the E2B(R3) field F.r.3.2 (as value).

     - If the E2B(R2) field B.3.1.d is not numeric (e.g., because of the presence of a qualifier), the content should be copied as is to the E2B(R3) field F.r.3.4.

  2) The unique E2B(R2) field B.3.2 should be copied into the E2B(R3) field F.r.3.4.

- To downgrade to E2B(R2), the following recommendations apply:

  1) The downgrade of the E2B(R3) fields F.r.3 depends on their content:

     - If the E2B(R3) field F.r.3.1 is set (coded value), it should be copied to the E2B(R2) field B.3.1.d.

     - If the E2B(R3) field F.r.3.1 is not set, the field F.r.3.2 (numeric value) should be copied instead.

     - If the E2B(R3) fields F.r.3.2 (numeric value) is qualified (e.g., as 'greater than'), the information that is copied to the E2B(R2) field B.3.1.d should be made up of the qualifier followed by the numeric value.

     - If the E2B(R3) fields F.r.3.1 and F.r.3.2 are not set, the free text field F.r.3.4 should be copied, truncated if appropriate.

- If both coded (F.r.3.1) and numeric (F.r.3.2) fields are set, the coded value should be copied to the E2B(R2) field B.3.1.d, and the numeric value (with qualifier and unit, if set) should be copied to the E2B(R2) field B.3.2 in the form of

    TEST <test name> (<date>) [RESULT: <result>]: <unstructured test results>

2) The test result fields of E2B(R3), i.e., F.r.2.1 (test name), F.r.1 (date) and F.r.6 (comments), should be concatenated into the E2B(R2) field B.3.2 (see pattern above).

    - If there is not enough space in the E2B(R2) field B.3.2, it should be truncated (see section 5.5 for instructions on the way to truncate fields) and the complete field value should be appended to the E2B(R2) case narrative field, i.e., B.5.1. The information should be preceded by the prefix 'TEST RESULTS'.

5.7.8 Drug and Dosage Information

E2B(R3) provides a different approach for the dosage information, which repeats for a given drug in E2B(R3). The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Dosage information	B.4.k.5	*unique per drug*	G.k.4.r	*repeatable per drug*

The general principle to support multiple dosage information in E2B(R2) is to repeat the drug section for each dosage, which implies repeating the drug section for each dosage information of the same drug.

The upgrade to E2B(R3), however, should not try to further structure the information, e.g., by grouping the dosage information for the same drug under a unique drug section. The dosage information should be upgraded to E2B(R3) as is.

The following recommendation applies:

- To upgrade to E2B(R3), the unique set of dosage information fields in E2B(R2) (fields B.4.k.3, B.4.k.5.1 to B.4.k.5.5, B.4.k.6, B.4.k.7, B.4.k.8, B.4.k.9, B.4.k.12, B.4.k.14 and B.4.k.15) should be copied into the dosage information in E2B(R3) of the corresponding

drug section. There should be no attempt to recombine the dosages below the same 'drug' element even if the constituents of the drug are the same.

- To downgrade to E2B(R2), a separate drug section (i.e., B.4.k) should be created for each dosage information of the same drug. For each drug section created during the conversion, the fields not related to dosage information should be filled with the same content.

  Example: Input in E2B(R3):

          Drug 1:

              Dosage Information: dosage A

              Dosage Information: dosage B

          Drug 2:

              Dosage Information: dosage C

              Dosage Information: dosage D

      Output in E2B(R2):

          Drug 1A: information on drug 1 and dosage A

          Drug 1B: information on drug 1 and dosage B

          Drug 2C: information on drug 2 and dosage C

          Drug 2D: information on drug 2 and dosage D

In addition, the E2B(R3) takes another approach regarding separate dosages. The E2B(R2) field for the number of separate dosages, i.e., B.4.k.5.3, has been deleted in E2B(R3). This calls for a set of conventions when converting dosage information between the two message formats.

The following recommendation applies:

- To upgrade to E2B(R3), the following cases can occur:
  1) The dose value and the number of separate doses are provided. In such case, the dose value in E2B(R3) should be multiplied by the number of separated doses. In addition, the number of separated doses should be appended to the E2B(R3) field G.k.4.r.8 (dosage text).

     Example:

         Input in E2B(R2):

             Dose: 2 mg

             Number of separated doses: 3

         Output in E2B(R3):

Dose: 6 mg

Dosage text: 3 separated doses

Formula:　　Dose (E2B(R3)) = Dose (E2B(R2)) x Number of separated doses

2) The dose value is provided but not the number of separated doses. In such case, the dose value in E2B(R3) should be the same as in E2B(R2).

Example:

Input in E2B(R2):

Dose: 2 mg

Number of separated doses: <not provided>

Output in E2B(R3):

Dose: 2 mg

Formula:　　Dose (E2B(R3)) = Dose (E2B(R2)) x 1

- To downgrade to E2B(R2), if the dose value is provided in E2B(R3), the same value should be used in E2B(R2), accompanied by a number of separated doses set to 1.

Example:

Input in E2B(R3):

Dose: 2 mg

Output in E2B(R2):

Dose: 2 mg

Number of separated doses: 1

5.7.9 Substance Strength

E2B(R3) supports the strength for the drug substance, which does not exist in E2B(R2). The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Strength	-	-	G.k.2.3.r.3a	10N
Strength unit	-	-	G.k.2.3.r.3b	UCUM Code
Additional information on drug (free text)	B.4.k.19	100AN	G.k.11	2000AN

The following recommendation applies:

- To upgrade to E2B(R3), the fields should not be set, as they do not exist in E2B(R2).

- To downgrade to E2B(R2), the E2B(R3) fields for substance strength and strength unit should be concatenated and copied to the E2B(R2) field for additional information on drug, i.e., B.4.k.19. If the value to copy exceeds the size limit of the field, truncation should apply as described in section 5.5.

Example:

Input in E2B(R3):

    Substance #1:

        Name: substance-1-name

        Strength and strength unit: 1 mg

    Substance #2:

        TermID: substance-2-term-id

        TermID version date / number: substance-2-version

        Strength and strength unit: 2 mg

Output in E2B(R2):

    Additional information on drug (free text):

        substance-1-name: 1 mg; substance-2-term-id (substance-2-version): 2 mg

5.7.10 Indication

E2B(R3) provides a different approach for the indication information, which repeats in E2B(R3). The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	Format	Field	Format
Indication	B.4.k.11	*unique per drug*	G.k.7.r	*repeatable per drug*

The general principle, when converting the information back to E2B(R2), is to focus on the first indication only. Each additional indication should be copied to the narrative section.

The following recommendation applies:

- To upgrade to E2B(R3), the unique indication for the drug should be copied to the indication section of the E2B(R3) message. If the E2B(R2) message contains multiple drug sections, for the same drug information but different indications, the information should be

copied as in E2B(R2) without any attempt to recombine the indication information under the same drug section.

- To downgrade to E2B(R2), the drug section should not be duplicated to support multiple indications. Instead, only the first indication should be copied from E2B(R3) back to E2B(R2). The other indications should then be copied into the narrative section, under the prefix 'INDICATION', extended with the name of the drug between parentheses. The content of the indication field should be composed of the drug indication as reported by the primary source (i.e., G.k.7.r.1), and the indication in MedDRA terminology along with the MedDRA version (i.e., G.k.7.r.2a and G.k.7.r.2b).

Example: Input in E2B(R3):

Drug 1: drug-1

2 Indications: indication-1a, indication-1b

Drug 2: drug-2

3 Indications: indication-2a, indication-2b, indication-2c

Output in E2B(R2):

Drug 1: drug-1

Indication: indication-1a

Drug 2: drug-2

Indication: indication-2a

<content of case narrative>

INDICATION   drug-1:   indication-1b   (MedDRA   code;   MedDRA version)

INDICATION   drug-2:   indication-2b   (MedDRA   code;   MedDRA version)

INDICATION   drug-2:   indication-2c   (MedDRA   code;   MedDRA version)

5.7.11 Drug-Reaction / Event Matrix

E2B(R3) provides a different approach for the drug-reaction / event matrix. The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Time interval (start – last)	B.2.i.7 B.4.k.13	*4 fields*	G.k.9.i.3	-
Drug recurrence (See section 4.2.12)	B.4.k.17	-	G.k.9.i.4	-
Drug reaction relatedness	B.4.k.18	-	G.k.9.i.1 G.k.9.i.2.r	-

The general principle of the upgrade to E2B(R3) is to combine the E2B(R2) fields for drug recurrence (i.e., B.4.k.17) and for drug-reaction relatedness (i.e., B.4.k.18) into the E2B(R3) field for drug-reaction matrix (i.e., G.k.9.i). The downgrade to E2B(R2) should focus on a single value for the time interval between drug administration and start of reaction / event (field B.4.k.13) in E2B(R2).

The following recommendation applies:

- To upgrade to E2B(R3), the approach is as follows:

    1) All the information related to the drug-reaction / event matrix should be listed in a unique table, ordered per reaction / event.

    2) An entry in the matrix for each reaction / event occurrence should be created.

    3) The time interval value from the first occurrence of the reaction / event in B.2.i should be retrieved.

    4) The recurrence flag for that particular reaction / event (see section 5.2.11) should be set.

    5) The assessment fields for that reaction / event should be iterated.

        Example:

            Input in E2B(R2):

                Drug:

                    Time interval (start – last): 10 days - 2 days

                    Recurrent administration: Yes

                    Drug recurrence: Event 1

                    Drug relatedness:

                        Event 1:   Source: reporter

<table>
<tr><td></td><td></td><td>Method: global introspection</td></tr>
<tr><td></td><td></td><td>Result: related</td></tr>
<tr><td></td><td>Event 1:</td><td>Source: company</td></tr>
<tr><td></td><td></td><td>Method: algorithm</td></tr>
<tr><td></td><td></td><td>Result: possibly related</td></tr>
<tr><td></td><td>Event 2:</td><td>Source: reporter</td></tr>
<tr><td></td><td></td><td>Method: global introspection</td></tr>
<tr><td></td><td></td><td>Result: not related</td></tr>
<tr><td></td><td>Event 2:</td><td>Source: company</td></tr>
<tr><td></td><td></td><td>Method: algorithm</td></tr>
<tr><td></td><td></td><td>Result: possibly related</td></tr>
</table>

Input in E2B(R3):

    Drug matrix for Event 1:

        Time interval (start – last): 10 days - 2 days

        Recurrent administration: Re-challenge was done, reaction recurred

<table>
<tr><td>Relatedness A:</td><td>Source: reporter</td></tr>
<tr><td></td><td>Method: global introspection</td></tr>
<tr><td></td><td>Result: related</td></tr>
<tr><td>Relatedness B:</td><td>Source: company</td></tr>
<tr><td></td><td>Method: algorithm</td></tr>
<tr><td></td><td>Result: possibly related</td></tr>
</table>

    Drug matrix for Event 2:

        Time interval (start – last): 10 days - 2 days

<table>
<tr><td>Relatedness A:</td><td>Source: reporter</td></tr>
<tr><td></td><td>Method: global introspection</td></tr>
<tr><td></td><td>Result: not related</td></tr>
<tr><td>Relatedness B:</td><td>Source: company</td></tr>
<tr><td></td><td>Method: algorithm</td></tr>
<tr><td></td><td>Result: possibly related</td></tr>
</table>

- To downgrade to E2B(R2), the approach is as follows:

1) The time interval for the first reaction / event listed in B.2.i should be retrieved.

2) For each reaction / event:

  ▪ The time interval for the first reaction to the drug section should be copied.

  ▪ The drug recurrence as in the matrix section (see section 5.2.11) should be set.

  ▪ If it recurs, i.e., when E2B(R3) field G.k.9.i.4 is set to 'Re-challenge was done, reaction recurred (yes-yes)', the corresponding reaction(s) / event(s) should be copied into the recurrence section.

  ▪ The assessment fields for that reaction / event should be iterated.

Example: *see above*

5.7.12 Additional Information on Drug

E2B(R3) provides a different approach for the additional information on the drug, which consists of repeatable coded values in E2B(R3) instead of a single free text field in E2B(R2). The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Additional information on drug (coded)	-	-	G.k.10.r	*11possible values*
Additional information on drug (free text)	B.4.k.19	100AN	G.k.11	2000AN

The following recommendation applies:

- To upgrade to E2B(R3), the E2B(R2) field B.4.k.19 should be copied into the E2B(R3) field G.k.11.

- To downgrade to E2B(R2), the E2B(R3) fields G.k.10.r, i.e., the meaning of the coded values, should be copied into the E2B(R2) field B.4.k.19, separated by commas. The field should be extended with the content of the field G.k.11, if any. If there is not enough space in E2B(R2) field B.4.k.19, the information should be truncated (see section 5.5) and the full information should be stored in the narrative section, under the prefix 'ADDITIONAL INFO ON DRUG'. The heading should be extended with the name of the drug between parentheses.

Example (with enough space in B.4.k.19):

  Input in E2B(R3):

Drug: drug-1

Codes: code-1, code-2

Other info: other-information

Output in E2B(R2):

Additional info: meaning-code-1, meaning-code-2, other-information

Example (with not enough space in B.4.k.19):

Input in E2B(R3):

Drug: drug-1

Codes: code-1, code-2, code-3, code-4, code-5

Other info: other-information

Output in E2B(R2):

Additional info: meaning-code-1, meaning-code-2, meaning-code-3…

Narrative section:

ADDITIONAL INFO ON DRUG (drug-1): meaning-code-1, meaning-code-2, meaning-code-3, meaning-code-4, meaning-code-5, other-information

5.7.13 Additional Sender Diagnosis

E2B(R3) provides a different approach for the additional sender diagnosis, which repeats in E2B(R3). The structural change impacts the following fields:

Description	E2B(R2)		E2B(R3)	
	Field	**Format**	**Field**	**Format**
Sender diagnosis	B.5.3	*unique*	H.3.r	*repeatable*

The following recommendation applies:

- To upgrade to E2B(R3), the field B.5.3 should be copied to the field H.3.r of E2B(R3).

- To downgrade to E2B(R2), the first occurrence of E2B(R3) field H.3.rshould be copied into the E2B(R2) field B.5.3. The other fields, if any, should be copied into the narrative section under the heading 'ADDITIONAL SENDER DIAGNOSIS'.

Example:

Input in E2B(R3):

Sender diagnosis #1: diagnosis-1, diagnosis-version-1

Sender diagnosis #2: diagnosis-2, diagnosis-version-2

Sender diagnosis #3: diagnosis-3, diagnosis-version-3

Output in E2B(R2):

Sender diagnosis: diagnosis-1, diagnosis-version-1

Narrative section:

ADDITIONAL SENDER DIAGNOSIS: diagnosis-2 (diagnosis-version-2), diagnosis-3 (diagnosis-version-3)

5.7.14 Batch and Message Wrappers

E2B(R3) provides a unique batch wrapper and a repeatable message wrapper, while the E2B(R2) guideline only provides a unique message wrapper.

Description	E2B(R2)		E2B(R3)	
	Section	**Characteristic**	**Section**	**Characteristic**
Batch wrapper	M.1	*unique*	N.1	*unique*
Message wrapper	-	-	N.2.r	*repeatable*

Although the E2B(R2) section M.1 is named 'message wrapper', it corresponds to a batch wrapper as it covers all the safety reports the message contains. Therefore, the following recommendations apply:

- To upgrade to E2B(R3), the following recommendations apply:

  1) The E2B(R2) section M.1 should be mapped to the E2B(R3) section N.1, with a one-to-one relationship (see related implementation guides), except for the elements covered in sections 5.2.2 (codes for the type of message), 5.3.2 (format version and release), and 5.1.3 (date of transmission).

  2) The E2B(R3) section N.2.rshould be filled with the following contents:
     - E2B(R3) field N.2.r.1 (message ID) with E2B(R2) field A.1.0.1
     - E2B(R3) field N.2.r.2 (message sender ID) with E2B(R2) field M.1.5
     - E2B(R3) field N.2.r.3 (message receiver ID) with E2B(R2) field M.1.6
     - E2B(R3) field N.2.r.4 (date of message creation) with E2B(R2) field A.1.3

- To downgrade to E2B(R2), the following recommendations apply:

  1) The E2B(R2) section M.1 should be mapped to the E2B(R3) section N.1, with a one-to-one relationship (see related implementation guides), except for the elements covered in sections 5.2.2 (codes for the type of message), 5.3.2 (format version and release), and 5.1.3 (date of transmission).

2) The E2B(R3) section N.2.rshould be ignored.

5.7.15 ICSR Message Sender and Receiver in ACK

E2B(R3) provides a different way to exchange ICSR message sender and receiver in the Acknowledgement message.

Description	E2B(R2)		E2B(R3)	
	Section	**Characteristic**	**Section**	**Characteristic**
ICSR Message Receiver	ACK: A.1.4	*unique*		
ICSR Message ACK Sender			ACK: ACK.B.r.4	*repeatable*
ICSR Message Sender	ACK: A.1.3	*unique*		
ICSR Message ACK Receiver			ACK: ACK.B.r.3	*repeatable*

Given that the ICSR message ACK follows the opposite route than the ICSR message itself, the identification of sender and receiver should be swapped. Therefore, the following recommendations apply:

- To upgrade to E2B(R3), the E2B(R2) fields for ICSR message sender should be copied to each occurrence of the ICSR message ACK receiver in E2B(R3). Similarly, the E2B(R2) fields for ICSR message receiver should be copied to each occurrence of the ICSR message ACK sender in E2B(R3).

- To downgrade to E2B(R2), the E2B(R3) fields for ICSR message ACK sender and receiver should be copied from the first occurrence of the message acknowledgement to the ICSR message receiver and sender fields in E2B(R2), respectively.