The Adverse Reactions and Interactions Section of a CCDS

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The Adverse Reactions section and the Interactions section are the most critical elements of a CCDS. They have to serve the needs of both:

- **Regulatory:** Use of CCDS to govern local labeling and risk communication through local labeling
- **Pharmacovigilance:** Reference information for case assessment and periodic reporting

This presentation will **first** focus on the regulatory aspects.

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When deciding which adverse phenomena to include in a CCDS as **ADVERSE REACTIONS FOR THE PURPOSES OF LABELING**, follow:

- Properly interpreted local regulations, guidelines and regulatory expectations
- Your “heart”

**Whichever kicks in first**

*It is very unlikely that you, in these days and times, will find a regulation or guideline preventing you from doing what is ethical.*
Adverse Reactions - The Key Question

The key question:

How confident do I have to be about a causal association between the use of my drug and an adverse phenomenon in order to accept it as an AR (or interaction) for the purposes of labeling?

In most countries, regulations and guidelines do not answer this question.

In 2 countries, regulations and/or guidelines provide an answer:

- EU
- US

Adverse Reactions - Causality Threshold

EU causality threshold:

- At least reasonable possibility

US causality threshold:

- Adverse Reactions section: reasonable [causal] association; some basis to believe
- Warnings and Precautions section: reasonable evidence of causal association
Adverse Reactions - Causality Threshold

EU causality threshold:

- At least reasonable possibility

Don’t confuse this with “reasonable possibility for the purposes of EU safety reporting”

US causality threshold:

- Adverse Reactions section: reasonable [causal] association; some basis to believe
- Warnings and Precautions section: as soon as reasonable evidence of causal association

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Further illustrated in FDA’s:
- 2006 Adverse Reactions Section Guidance
- “Safety Reviewer Guidance”

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Further illustrated in FDA’s:
- preamble to the 2008 CBE Rule
- draft 2006 WP,CJ and BW Guidance
For

• Canada
• Japan

refer to the Adverse Reactions Section Comparison Table provided at the December 2010 DIA Labeling Conference.

The following is based on answers provided by Canada, EU, Japan and US in AR Comparison Table provided at the December 2010 DIA Labeling Conference.

• For adding an AR, is it required that a causal association seems proven? All 4 agencies: NO
• For adding an AR, is it required that a causal association seems well established? All 4 agencies: NO
• For adding an AR, is it required that a causal association seems highly likely? All 4 agencies: NO
• For adding an AR, is it required that a causal association seems more likely than not? 3 agencies: NO - FDA refers to “reasonable association”
• For adding an AR, is a mere temporal association sufficient? All 4 agencies: NO

This table contains many more gems. A MUST READ.
Today, for all practical purposes, there is remarkable similarity in regulatory expectations between Canada, EU, Japan, and US.

- Remarkably similar but not identical.
- In specific situations, assessments can vary significantly, both between and within agencies (just as between and within companies).
  - Decisions involve a significant degree of judgment.
  - Levels of concern may differ.

Can we populate the Adverse Reactions section of a CCDS with ARs (NOT frequency info) that we can submit to all agencies without embarrassing ourselves?

YES, if we do it right!

The relevance of an adverse phenomenon (for individuals and from a public health perspective) is taken into consideration when deciding at which level of confidence about causation the phenomenon is accepted as an AR for purposes of labeling.

This is a general (global) "legal" principle.

- See FDA’s 2006 AR Section Guidance and the answers provided in the AR Comparison Table provided at the December 2010 DIA Labeling Conference.
- This principle is also illustrated in the CIOMS III/V book.
Adverse Reactions - Relevance Threshold

The relevance of an adverse phenomenon (for individuals and from a public health perspective) is taken into consideration when deciding at which level of confidence about causation the phenomenon is accepted as an AR for purposes of labeling.

This is a general (global) “legal” principle.

- See FDA’s 2006 AR Section Guidance and the answers provided in the AR Comparison Table provided at the Oct 2010 DIA Labeling Conference.
- This principle is also illustrated in the CIOMS III/V book.

Note: The relevance of a risk (in terms of severity, irreversibility, proportion of patients affected, need for precautionary measures etc.) plays a key role when deciding whether to present the risk in a more prominent location, such as in Warnings and Precautions.

This will be discussed in a later presentation.

In-depth Review of Definitions

The following slides are about a few must-knows for labeling/regulatory, pharmacovigilance and clinical/medical professionals.
Adverse Reaction Definitions - Safety Reporting

1. Definition/interpretation in ICH E2A
2. FDA’s definition/interpretation for IND safety reporting
3. EU definition for “IND safety reporting”

ICH E2A: CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING (1994)

II. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

A. Basic Terms

2. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase “responses to a medicinal products” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products, a well accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.
Adverse Reaction Definitions - Safety Reporting

Universe of Safety Reporting

1. Definition/interpretation in ICH E2A

ICH E2A: CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING (1994)

II. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

A. Basic Terms

2. Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with therapeutic dose(s) may not be established:

Note: Reasonable possibility = causal relationship cannot be ruled out

Imagine we would use this interpretation of “adverse reaction” for labeling and listed as adverse reactions all events, for which we cannot exclude a causal association.

The phrase “responses to a medicinal product” means that a causal relationship to the medicinal product and an adverse event is at least a reasonable possibility, i.e., a reasonable causal relationship.

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

…

III. STANDARDS FOR EXPEDITED REPORTING

A. What Should be Reported?

1. Single Cases of Serious, Unexpected ADRs

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as “plausible relationship,” “suspected causality,” or “causal relationship cannot be ruled out” are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression “reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.
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2. FDA’s definition/interpretation for IND safety reporting

2010 IND Safety Reporting Rule (final)

"Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

Corresponding 2010 Draft Guidance

"An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event."
3. EU definition for “IND safety reporting”

**Directive 2001/20/EC**

Adverse reaction: All untoward and unintended responses to an investigational medicinal product related to any dose administered.

**2011 Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use**

Point 48:
The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Implied:

\[ \text{Adverse Reaction} = \text{Suspected Adverse Reaction} = \text{Adverse Reaction} \]

We will see that one of the keys to the difference between “adverse reaction for the purposes of IND safety reporting” and “adverse reactions for the purposes of labeling” lies in who decides that there is a reasonable possibility of a causal relationship.
Adverse Reaction Definitions - Labeling

... for the purposes of labeling

- Two Regulators provide a definition/interpretation of “adverse reaction” for the purposes of labeling
  1. USA (provides very detailed guidance)
  2. EU (provides less detailed guidance)

Adverse Reaction Definitions - Labeling: US

... for the purposes of labeling

- US

201.57(c)(7) 6 Adverse reactions.

For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

201.80(g) Adverse Reactions.

An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

FDA illustrates the meaning of the concepts “reasonable causal association” and “some basis to believe”... by providing examples of how to decide if an event should be included in labeling as an adverse reaction.

See FDA’s 2006 Adverse Reactions Section Guidance
### Adverse Reaction Definitions - Labeling: EU

... for the purposes of labeling

- EU

**2009 SmPC Guideline**

4.8 Undesirable effects

This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC.

The content of this section should be justified in the Clinical Overview of the marketing authorisation application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. ...

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### Reasonable Possibility

Now, we have to talk in more depth about the concept “reasonable possibility”.

... another source of potential confusion ...
ICH E2A: ...

FDA IND safety reporting: ...

EU “IND safety reporting”: ...

... for the purposes of EU labeling

EU SmPC guideline: ...

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ICH E2A:

Causal relationship cannot be ruled out

Existence of a “reasonable possibility” of causation turns a reported adverse event into a (suspected) AR.

Decision made by: Company

Clarified by 3 examples

1. type of event has strong association with drug exposure; even if only 1 event reported
2. type of event not commonly associated with drug exposure, but uncommon in exposed population; possibly even if only 1 event reported
3. Aggregate analysis shows higher frequency than in concurrent or historical control group

EU “IND safety reporting”:

Existence of a “reasonable possibility” of causation turns a reported adverse event into a (suspected) AR.

Decision made by: Investigator (usually)

There are facts (evidence) or arguments to suggest a causal relationship
ICH E2A: Causal relationship cannot be ruled out

FDA IND safety reporting: Decision made by: Company
Clariﬁed by 3 examples

EU “IND safety reporting”: Decision made by: Investigator (usually)
There are facts (evidence) or arguments to suggest a causal relationship

... for the purposes of EU labeling

EU SmPC guideline: Decision made by: Company and/or Regulator
Based for example, on their comparative incidence in clinical trials, or on ﬁndings from epidemiological studies and/or on an evaluation of causality from individual case reports
Based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality

In-depth Review of Deﬁnitions - CONCLUSIONS

1. There is ample opportunity for confusion.
2. A (suspected) adverse reaction for the purposes of safety reporting is not necessarily an adverse reaction for the purposes of labeling.
3. Avoid spill-over of interpretations from the universe of safety reporting to the universe of labeling.
4. YOU (company) and the agencies, but not investigators, decide what is included in labeling as an adverse reaction.
5. When deciding to accept a phenomenon as an adverse reactions for the purposes of labeling, the following 2 aspects play an important role:
   - the level of conﬁdence in the existence of a causal association
   - the relevance of the phenomenon for the product user
Anticipated Adverse Reactions

Where to include anticipated* risks?

For the CCDS, this depends on your company-internal rules.

For example:

- If anticipated from “class”: in the Adverse Reactions section (if warning-worthy, they may also be addressed in W&P)
- If anticipated based on non-clinical data: In a non-clinical safety section or other appropriate section (e.g., Pregnancy)

*Not everything anticipated during development will end up as anticipated risks/reactions/interactions in labeling

Adverse Reactions - Which Section?

It is considered best practice to have ALL adverse reactions (observed and anticipated) listed in the Adverse Reactions section.

This means: Even those adverse reactions that are discussed in Warnings and Precautions are still listed in the Adverse Reaction section.
Labeling and Safety Specification

What is the relationship between an ICH SAFETY SPECIFICATION’s “important identified risks” and “important potential risks” and the risks described in labeling?

• Important identified risks = appear in labeling as important adverse reactions/interactions
• Important potential risks = inconsistent approaches, resulting from apparent lack of agreement on the meaning of the terms “identified risk” and “potential risk” vis-à-vis the criteria for adopting items as adverse reactions for the purposes of labeling.
  - Is an identified risk a proven risk? Then all other important labeled risks would appear under potential risks.
  - Is a potential risk just a signal that needs follow up? Then they would typically not appear in labeling at all (or just under, e.g., preclinical tox)

Also part of the Safety Specification:

• Identified and potential interactions and Pharmacological class effects = in labeling if they cross the threshold (IA only if also clinically relevant)

Safety Specification and the SmPC

The Summary of the safety profile of SmPC section 4.8 should be consistent with the important identified risks mentioned in the Safety Specification of the Risk Management Plan.

Consistent does not necessarily mean complete duplication or identical granularity.
Adverse Reaction Frequencies

While local labeling regulations, guidelines and regulatory expectations, properly interpreted, provide a good basis for deciding which phenomena to add to a CCDS (CCSI) as ARs for the purposes of labeling, …

… the local approaches to illustrating the probability of ARs differ so much that, for the most part, no ONE solution fits all.

There are various ways of dealing with this situation in a CCDS.

1. Give every affiliate what they need
   Large table with both “EU frequency terms” and percentages.
   Percentages may have to be based on different data sets for, e.g., Canada, Japan, US.

2. Serve the “most needy” affiliates only
   Only “EU frequency terms”

3. Something in between

   Note: Some companies provide EU frequency terms PLUS - for reasons of transparency - the percentages behind the terms (or other rationales for choosing a category, e.g., Rule of 3). These percentages are not necessarily implementable because the countries that use percentages in their local labels may use different data sets.
Adverse Reactions Section Structure

Separating Clinical Trials Experience from Postmarketing Experience from Class/Moiety reactions?

- Presenting clinical trials experience in a separate table/subsection (as in, e.g., US) is possible.
- Can work well (over time), if CCDS is created early in life cycle.
- Can mean a lot of hassle if the CCDS is created for an “old” product.

NOT separating Clinical Trials and Postmarketing Experience can be more “economical” and, if done wisely, does not diminish the value of the CCDS.

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Adverse Reactions Section - Mandatory Elements

Typically, not all information provided in the Adverse Reaction section can be implemented everywhere. Example: EU frequency terms, description of clinical data set

How do I show what I expect every affiliate to (try to) implement? In other words: How do I show what is my CCSI (“mandatory safety information”)?

Answer: Highlight what is mandatory by, e.g., bold face.

Some people find such highlights ugly. But that’s still better than all the email traffic or inconsistent implementation that results from the absence of highlights.

Adverse Reactions Terminology

Provide a list of ARs with terms suitable for risk communication.

- No poorly organized list of terms
- No list optimized for “listedness checking”
- A phenomenon caused by your product may have been reported with various names, and coded into various MedDRA PTs. It is still the same phenomenon.
- Diagnose what your product can cause, and represent the phenomenon with the best term.
- The best term to communicate a risk does not necessarily change when MedDRA changes.
- Following the MedDRA LLT → PT relationship does not necessarily give you the best term.
- Consider providing an attachment to the CCDS that translates the terms you consider best for risk communication into one or more MedDRA PTs (which then can be updated when MedDRA changes).
Adverse Reactions Terminology

Invest a lot of thought in identifying the phenomena to be listed as
1. ARs and
2. mere symptoms/manifestations or cascade events/complications.

- Decide to what extent to list symptoms/manifestations or cascade events/complications (e.g., to illustrate the potential severity of reactions). There should be a reason for including them other than establishing listedness.

- When including symptoms/manifestations or cascade events/complications make sure you create/maintain. There are several ways to accomplish this: Footnoting, explanatory text following the table or in W&P. Try to find a solution that also works in local labels or, at the very least, makes it easy for your affiliates to translate it in local labeling.
Adverse Reactions Terminology

To adjust granularity use …

1. the “diagnosing” approach discussed earlier, and

2. hierarchical term grouping (use of superordinate concepts, “group terms”)

- Hierarchical term grouping may cause loss of specificity (from a risk communication perspective). You may have to make up for it by, e.g., providing some specific, serious manifestations in a “footnote”.
- MedDRA HLTs are rarely specific enough for effective risk communication.
- You might find good group terms at the PT or LLT level, or have to “invent” them.

Interactions - Clinical Relevance/Significance

Expectation: Include in local labeling interactions that are clinically relevant/significant.

A pragmatic (and conservative) interpretation for core labeling is:

• Those interactions that may cause an adverse reaction, increase the likelihood or severity of an adverse reaction or, e.g., impair the effectiveness of one or both interactors.

Local labeling expectation: Provide advice on what to do about an interaction. For pale advice (such as a simple “use with caution”), you could consider to leave it out of your CCDS and let your affiliates decide locally what to say. → Risk of disharmonization
Interactions - Causality Threshold

Causality threshold for adverse interactions

- Same principles as for adverse reactions
- No proof or studies or human cases required

Pharmacodynamic Interactions

The Interactions section should list both pharmacokinetic and pharmacodynamic interactions

The problem:
Pharmacodynamic interactions can be borderline or clearly “trivial” if they describe mere additive effects.

There are no robust schematic rules for separating trivial from non-trivial pharmacodynamic interactions that also guarantee that a reader's reasonable information needs are met.

The solution:
Base your decision on reasonable reader expectations.
Interactions - Which Section?

What to include in INTERACTIONS and what in CLINICAL PHARMACOLOGY?

Depends on your company-internal rules (need to allow your affiliates to deviate based on local expectations).

• Clinical Pharmacology: Details on interaction studies. Info about interaction studies conducted to characterize metabolism.

• Interactions: Clinical conclusions on clinically relevant/significant interactions (or the absence thereof, if important), with appropriate advice.

Interactions - Which Section?

What to include in CONTRAINdications or WARNINGS AND PRECAUTIONS?

Depends on your company-internal rules (need to allow your affiliates to deviate based on local expectations).

• Contraindications: Strictly contraindicated combinations

• Warnings and Precautions:
  Approach 1: Keep interactions that come with “warnings”, precautions or “relative contraindications” in Interactions only
  Approach 2: Include warning-worthy interactions in Warnings and Precautions. (That an interaction comes with a precaution may not be sufficient for elevating it, because nowadays all interactions might come with at least a “caution …”)

• Always keep ALL interactions mentioned in Interactions
Interactions Section - Mandatory Elements

Consider highlighting (e.g. by bold face) those elements of interaction information that is considered mandatory for implementation (CCSI)

Examples of optional elements may include:

- Details of interaction studies (if included at all)
- Trivial advice
- Illustrating examples of interacting agents (e.g., long lists of CYP3A4 substrates)

Adverse Reactions and Interactions - Specific Pops

Should I have formal Specific Populations subsections in my Adverse Reactions or Interactions section? Or at least a formal Pediatric Population subsection?

- Get used to it. Alternatively, use the Specific populations section of your CCDS (if you have one).

Generally, if you do not want that your affiliates generate their own safety information (or make affirmative statements about the absence of risks) try to meet proactively the information needs of your affiliates.

There are various approaches to prevent propagation of optional information into labels where it is not appropriate.
Pharmacovigilance Needs

• Complete listing of adverse reactions and interactions

• Terminology which allows easy determination of listedness (ideally at the PT level)

• Information on, e.g., specific manifestations or severe outcomes

Issue:

Presentation and granularity optimized for pharmacovigilance assessment purposes is not necessarily an optimal template for risk communication in local labeling.

Possible solutions:

1. Attachment with PTs considered covered by terms in the Adverse Reactions and Interactions section
2. Consider stating severity and other particulars of important reactions, if at all necessary, in statements that elaborate on the risks (e.g., in W&P or below AR table in the AR section)