PROPOSED REVISIONS OF ISO 14155

ALIGNMENT WITH THE NEW EUROPEAN MEDICAL DEVICES DIRECTIVE

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Speaker’s perspective

• Former clinical investigator

• Work with clients regarding clinical study design, regulatory notifications, Ethics Committee requirements, adverse event reporting, clinical evaluations for CE marking and other activities

• New member of the ISO/TC 194 Working Group 4, which is developing the revision of standard ISO 14155
**Presentation Outline**

1. Introduction
2. Overview of the new Medical Devices Directive (MDD) provisions for clinical data
3. Head-to-head comparison of new MDD requirements and proposed ISO 14155 revisions
   - Definition of clinical data
   - Risk of use error
   - Technical knowledge / Training
   - Clinical evaluation
   - Adverse events
4. Opportunities for the manufacturer

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**Harmonized standards**

MDD 93/42/EEC, Art. 5: Compliance with EU harmonized standards, carries a presumption of conformity with the Directive's Essential Requirements (ER)

**EN ISO 14155:2003 is a HARMONIZED STANDARD**

Manufacturers can use this standard to achieve compliance with MDD requirements for clinical investigations
Regulatory developments in the EU

Revision of the MDD and AIMDD:

The revision of ISO 14155 is still ONGOING....

This presentation is based on the CURRENT status of the ISO 14155 revision, which may be subject to further changes.

New MDD / AIMDD and proposed ISO 14155

The new Directives contain significant changes regarding clinical data

The ISO 14155 revision process is an important opportunity for aligning the standard with the new MDD / AIMDD requirements and enhancing their implementation.
Overview of new requirements for clinical data

Pre-market studies
- Clinical data to support conformity with ERs for safety & performance

Post-market studies
- Consolidate claims and gather data on Incidents & Near-Incidents

Reimbursement

RELEVANT PARTS OF THE MDD

- Annex I: Essential Requirements
- Annex X: Clinical evaluation
- Article 10: Incidents
- Article 15: Clinical investigations
- Art. 14a: European databank
Important reference documents related to the new MDD provisions concerning clinical data

These guidance documents:
- contain certain terminology that is reported in the new Directive
- are useful for understanding some of the changes

Definition of CLINICAL DATA
[New MDD Article 1, Definitions, scope]
**Definition of clinical data**

**NEW DEFINITION in new MDD Art. 1**

- ‘clinical data’ means the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:
  - clinical investigation(s) of the device concerned; or
  - clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated;
  - published and/or unpublished data on clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.

**Definition of clinical data**

**PROPOSED ISO 14155**

- The definition of CLINICAL DATA is **NOT** included in the current version of revised ISO 14155.
- Development of clinical data is addressed in ISO 14155 in Annex A, Suggested procedure for literature review
  - Text is similar to ISO 14155:2003, except for the deletion of A1. Introduction
- Use of selected literature is based on several criteria including similarity in intended use, population, conditions of use, etc.
- Requires an assessment of the significance and weight of studies with different designs and of “published” and “unpublished” studies.
**Definition of clinical data - Implications**

<table>
<thead>
<tr>
<th>New MDD Art. 1</th>
<th>Proposed ISO 14155</th>
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<tbody>
<tr>
<td>New definition of ‘clinical data’ in Art. 1 will help avoid confusion between clinical investigations and other clinical data</td>
<td>The new MDD definition is not included</td>
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<tr>
<td>New definition is quite stringent and requires “demonstration of equivalence” to support data applicability (same as in MEDDEV 2.7.1)</td>
<td>The criteria for literature selection are less stringent: it is recognized that selected literature may be applicable to a variable extent and the term “similarity” is used (versus “equivalence”)</td>
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**COMMON ELEMENT:** Inclusion of “unpublished data” promotes harmonization with US since FDA requires the submission of unpublished as well as published clinical data (PMA regulations, 21 CFR Part 814)

**Risk of use error and training**

[New MDD Annex I, Essential Requirements]
MDD ERs: risk of use error, training

New MDD Annex I – General Requirements

I. GENERAL REQUIREMENTS

1. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients [...omissis...]

This shall include:

– reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and

– consideration of the technical knowledge, experience, education and training and, where applicable, the medical and physical conditions of intended users (design for lay, professional, disabled or other users).

PROPOSED ISO 14155

RISK OF USE ERROR

The relevant section is: Sec 4.3, Risk assessment

• Focus on medical risks to patients
• Use error is not mentioned
• Reference is made to ISO 14971

TECHNICAL KNOWLEDGE / TRAINING

The relevant section is: Sec 7, Responsibilities of sponsor

• Prior to commence the study, the sponsor shall ensure documentation of training, experience, scientific and/or clinical knowledge for all parties involved, including training on device use, clinical investigation brochure and protocol, CRFs, informed consent, sponsor procedures, GCPs and regulatory requirements
MDD ERs: risk of use error, training - Implications

- New MDD and revised ISO 14155 are aligned regarding the risk of use error and the need for training
- Companies will need to evaluate requirements for user training in a more formal manner
- New requirement regarding the need to reduce risks related to use error places more explicit responsibilities on companies to evaluate the device design and instructions for use to reduce these types of risks
- Requirements for risk analysis, including human factors, are strengthened by this change

Clinical Evaluation
MDD Annex I: Clinical evaluation

NEW ESSENTIAL REQUIREMENT

6a. Demonstration of conformity with the essential requirements must include a “clinical evaluation” in accordance with Annex X

COMMENT

• The new Directive reinforces the need for ALL devices, including class I, to include a clinical evaluation

• Although already implied in the original Directive, this need was seen as a weak area of implementation

MDD Annex X: Clinical evaluation - Overview of changes

• Amendments to Annex X include not only clarifications, but also new requirements

• Section 1, General provisions - significantly expanded
  – Increased emphasis on clinical data evaluation as the critical element to demonstrate conformity with the essential requirements of safety and performance

• Section 2, Clinical investigation - changes are more limited and mostly related to the reporting of adverse events
New MDD concepts for clinical evaluation

Device Technical documentation

Clinical data

Definition: Safety and/or performance information that is generated from the use of the device (NEW Art. 1)

Clinical investigations (Annex X Sec. 2)

Results of all clinical investigations

Relevant scientific literature

Demonstration of equivalence to the device in question is required for data obtained with a similar device (NEW Annex X Par. 1.1.1)

CLINICAL EVALUATION (NEW Annex X Sec. 1)

Required for demonstration of conformity with the ERs (NEW Ann. I Par. 6.2)

Must be fully documented and included in the technical documentation (NEW Ann. X Par. 1.1.b)

Must be actively updated with post-market surveillance data (NEW Ann. X Par. 1.1.c)

Guidance that supports new MDD requirements

EUROPEAN GUIDANCE DOCUMENT
MEDDEV 2.7.1, Evaluation of clinical data

- Aids in compliance with the proposed new provisions of the MDD regarding:
  - Development of adequate clinical evaluation reports and clinical risk analysis documentation
  - Preparation of complete and scientifically valid clinical investigation dossiers when clinical studies are required
  - Planning appropriate post-market surveillance programs covering clinical studies or justifying why this is not needed
**MDD changes: Clinical evaluation**

**PROPOSED ISO 14155**

Need to distinguish between *clinical evaluation* in the MDD and **Annex A, Suggested procedure for literature review** in ISO 14155

- Literature review in ISO 14155 Annex A provides evidence for justification and planning of the clinical study and not for demonstration of conformity.

- This procedure does not correspond to "clinical evaluation" as per Annex X
Current issues related to use of revised ISO 14155 in complying with new Annex X

**General provisions**

- The term “clinical evaluation” is not addressed in the current revised version of ISO 14155
- Therefore, the current version of the standard is not fully aligned with the revised General Provisions in Annex X of the new MDD
- Given the emphasis of the new Directive on clinical evaluation, these issues should be taken into consideration in the ISO 14155 revision process
Adverse event reporting
[New MDD Annex X, Clinical Evaluation]

The next slides concern adverse events and will describe:

- **Current MDD Directive (93/42/EEC)**
  - Types of adverse events (AEs) to be reported
  - European Guidance on reporting AEs (MEDDEV 2.12-1), which does not apply to AEs during clinical studies
  - ISO 14155 covers AEs during clinical studies

- **New Directive**
  - New requirements for AE reporting during clinical studies
  - Revised ISO 14155: alignment with new MDD
  - Role of sponsor, investigator, monitor
  - Format & contents of AE reports
CURRENT MDD Requirements for adverse events

ISO 14155
- Parties involved:
  - Sponsor
  - Investigators
  - Monitors
  - Ethics Committees
  - Competent Authorities

MEDDEV 2.12-1 Vigilance Guidance
- Parties involved:
  - Manufacturer
  - Users and others concerned with the continuing safety of medical devices
  - Competent Authorities
  - European Commission

ADVERSE EVENTS - OVERVIEW
- MDD Requirements
  - Article 10 (postmarket incidents)
  - Annex X (clinical investigations)

Post-market incidents
- AEs during clinical studies
MDD (93/42/EEC): Events to be reported

INCIDENT-NEAR INCIDENT (MDD, Art. 10)
any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which might lead to [called a “near incident”] or might have led to [called an “incident”]
- the death of a patient or user, or
- to a serious deterioration in his state of health

This definition of events to be reported applies to BOTH events occurring during clinical investigations AND post-marketing

MEDDEV 2.12-1 Rev. 4 (April 2001)
Identification of incidents to be reported
MEDDEV 2.12-1 Rev. 4 (April 2001)
Medical device vigilance – incident response

Note: This diagram does not specify the role of other parties, such as the European Auth. Rep, the medical practitioner, or medical institutions.

MEDDEV 2.12-1 Rev. 4 (April 2001)
Suggested Competent Authority report format
MEDDEV 2.12-1 Rev. 5

• Publication awaited within weeks
• Extensive revision from the previous version (April 2001)
• Some ideas taken from the publications of GHTF Study Group 2
• Some of the main changes are:
  – Changes in basic terminology
  – Inclusion of new definitions
  – Stricter on the timescale for reporting incidents
  – New concepts: ‘periodic summary reporting’ and ‘trend reporting’

• Templates (Annexes):
  – Manufacturer’s incident report form
  – Field Safety Corrective Action (FSCA) report form
  – Field Safety Notice
  – Form for exchange of information between national CAs

ISO 14155 definition – alignment with MDD (93/42/EEC)

Type of AE that the MDD requires to be reported corresponds to the ISO 14155 definition of serious adverse device effect

serious adverse device effect: adverse device effect that resulted in any of the consequences characteristic of a serious adverse event* or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

* These consequences are death or serious health deterioration, as specified in the ISO 14155 definition of serious adverse event
NEW DIRECTIVE

Requirements for adverse events

NEW DIRECTIVE ANNEX X

2.3.5. All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.
### Revised ISO 14155: alignment with new MDD

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<td>2.3.5. <strong>All serious adverse events</strong> must be fully recorded and immediately notified to <strong>all competent authorities of the Member States in which the clinical investigation is being performed</strong></td>
<td>Par. 7.5 (c) “The sponsor shall, if required, report any adverse events to the regulatory authorities in the country where the clinical investigation is conducted”</td>
</tr>
</tbody>
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**ISO 14155 is not aligned with the new MDD**
- ISO 14155 extends reporting to all adverse events (*vs. only serious AEs in MDD*)
- Timeframes for reporting are not specified (*vs. immediately in MDD*)
- Notification in the country (*vs. all countries in MDD*) where the study is conducted

### Revised ISO 14155: Responsibilities of sponsor, investigator and monitor related to AE reporting

**SPONSOR**
- Review investigator assessment
- Determine relationship with the device
- Ensure timely reporting to EC
- Notify competent authorities
- Report to DMC and ensure timely review
- In multicenter studies, inform all investigators of all SAEs
- Inform ECs and CAs of significant new safety information

*Note: some statements may be revised for alignment with the new MDD which requires reporting of ALL SAEs to the regulatory authorities*
Revised ISO 14155: Responsibilities of sponsor, investigator and monitor related to AE reporting

INVESTIGATOR
- report SAEs immediately to the sponsor
- report SADEs to ECs
- report SAEs to CAs if required by national regulations or clinical investigation plan, whichever is more stringent
- supply sponsor with any additional information related to the safety reporting upon request

Note: some statements may be revised for alignment with the new MDD which requires reporting of ALL SAEs to the regulatory authorities

MONITOR
- Verify that all AEs are reported to the sponsor
- Verify that all SAEs and SADEs are immediately reported to the Sponsor, ECs and regulatory authority(ies), as required

Revised ISO 14155
Adverse event: format & contents of reports

- The type of AE information, which is provided by the investigator and/or sponsor to the Ethics Committee(s) / Competent Authority, is an important aspect as it relates to the reviewers’ ability to evaluate the meaning of the event

- This issue is not addressed in the current revision of ISO 14155
  - Unlike MEDDEV 2.1.12, the revised ISO 14155 does not provide guidance on how events should be reported
  - No template for report format & content is included
  - No flow chart of the reporting process is presented

FDA published a new draft guidance on this topic, see next slide
Importance of HOW adverse events are reported

Guidance for Clinical Investigators, Sponsors, and IRBs
Adverse Event Reporting — Improving Human Subject Protection
April 7, 2007

New draft FDA guidance addresses concerns raised by the IRB community that it receives “large volumes of individual adverse event reports – often lacking in context and detail” that it cannot adequately assess.

- FDA guidance proposes that sponsors and investigators need not provide every adverse event it receives to IRBs.
- FDA concludes that, in most cases, an individual adverse event report cannot be assessed unless it is accompanied by an analysis that explains why the event “represents a ‘problem’ for the study and why it is ‘unanticipated’.”

Summary - Implications of new requirements for adverse event reporting

- New MDD eliminates the cross-reference to Article 10 (incidents –near incidents) for events which must be reported during clinical investigations
  - Thus, it will not be possible to easily apply the Vigilance guidance MEDDEV 2.12-1 as was done in the past

- Revised ISO 14155:
  - is not yet fully aligned with the new Directive
  - aids in understanding the roles of the various parties, including the sponsor, investigator, monitor and Ethics Committee
  - does not include guidance on the manner in which events should be reported or templates that can be used

- Further revisions of ISO 14155 may address these open issues as well as alignment with the new MDD
ISO 14155 Revision – What can we expect?

• Extensive work by ISO TC 194 Working Group 4 has resulted in the development of a revised ISO 14155 standard that clearly outlines the steps needed for proper conduct of device clinical investigations

• The current revision of ISO 14155 provides the needed detail for meeting most of the clinical data requirements of the new Directives; however, additional changes should be considered to ensure full alignment
Is the purpose of ISO 14155 to carry the full weight of the new Directive?

Revised ISO 14155

Opportunities for the manufacturer (I)

• When the new Directives are adopted, they will help clarify requirements, thereby addressing existing concerns related to the clinical data review and evaluation process
  – flexibility will remain regarding the amount of data needed

• Points that need special attention
  – Risk analysis
  – Documentation of clinical evaluation
  – Design of clinical investigations
  – Implementation of post-market surveillance and follow-up programs
Opportunities for the manufacturer (II)

- Additional clinical guidelines are available, which should be used to prevent compliance problems which can impact both products already marketed, and those being developed for future marketing

- Device manufacturers should keep informed on the ISO 14155 revision process and its full alignment with the new European requirements for clinical data

Questions?

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