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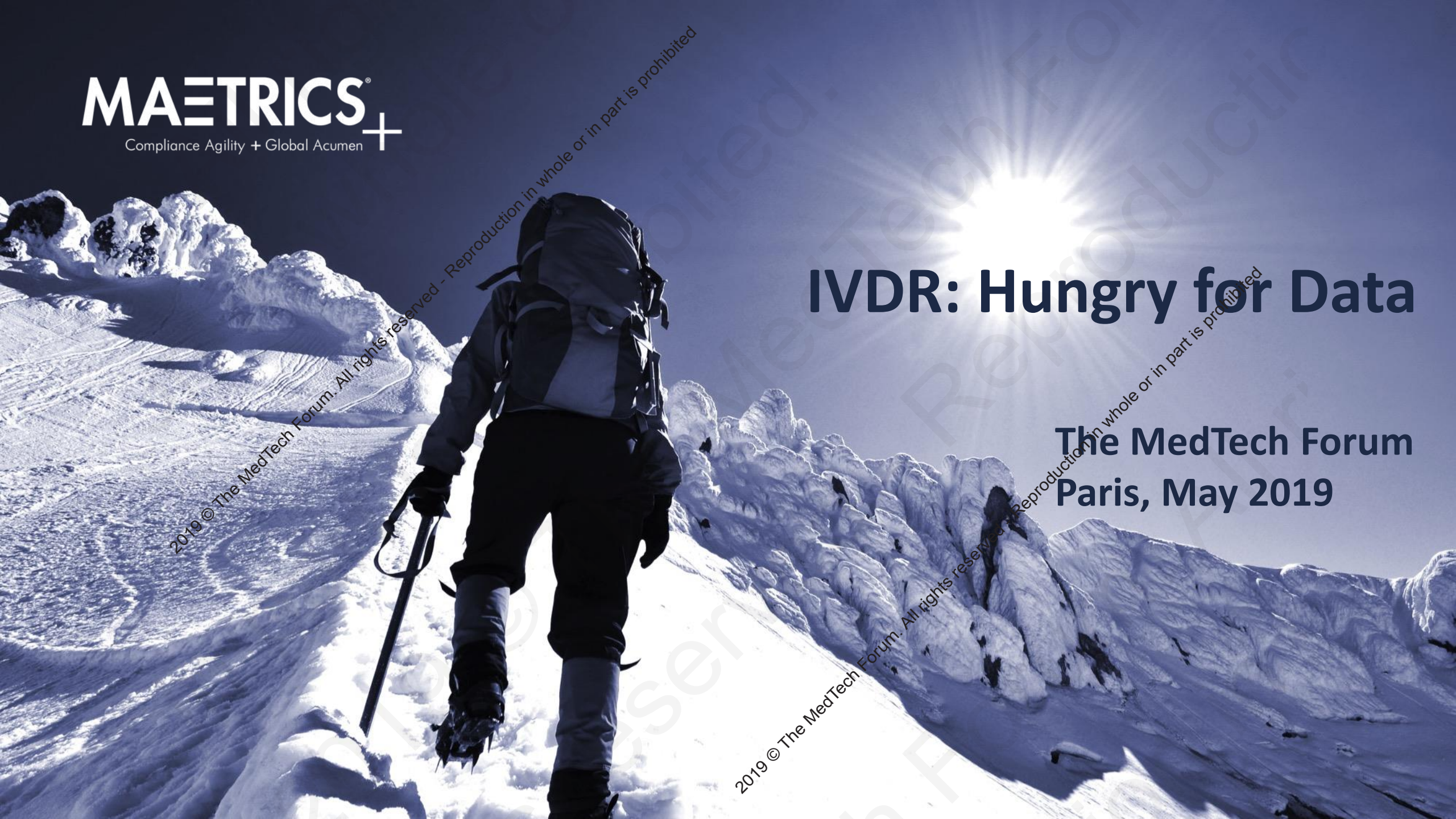

IVDR: Hungry for Data

The MedTech Forum
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Agenda

1. Introduction
2. Established Products
3. Generating Data
4. Practical Considerations

CHAPTER VI

CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56

Performance evaluation and clinical evidence

1. Confirmation of conformity with relevant general safety and performance requirements set out in Annex I, in particular those concerning the performance characteristics referred to in Chapter I and Section 9 of Annex I, under the normal conditions of the intended use of the device, and the evaluation of the interference(s) and cross-reaction(s) and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, ***shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III***.

The manufacturer shall ***specify and justify the level of the clinical evidence necessary*** to demonstrate conformity with the relevant general safety and performance requirements. That level of ***clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose***.

To that end, manufacturers shall plan, conduct and document a performance evaluation in accordance with this Article and with Part A of Annex XIII.

CHAPTER VI

CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56

Performance evaluation and clinical evidence

2. The ***clinical evidence shall support the intended purpose*** of the device as stated by the manufacturer and be based on a continuous process of performance evaluation, following a performance evaluation plan.

CHAPTER VI

CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

Article 56

Performance evaluation and clinical evidence

3. A performance evaluation shall follow a defined and methodologically sound procedure for the demonstration of the following, in accordance with this Article and with Part A of Annex XIII:

(a) scientific validity;

(b) analytical performance;

(c) clinical performance.

The data and conclusions drawn from the assessment of those elements ***shall constitute the clinical evidence for the device***. The clinical evidence shall be such as to scientifically demonstrate, by reference to the state of the art in medicine, that the intended ***clinical benefit(s)*** will be achieved and that the device is safe. ***The clinical evidence derived from the performance evaluation*** shall provide scientifically valid assurance, that the relevant general safety and performance requirements set out in Annex I, are fulfilled, under normal conditions of use.

CHAPTER VI

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Article 56

Performance evaluation and clinical evidence

4. ***Clinical performance studies*** in accordance with Section 2 of Part A of Annex XIII ***shall be carried out*** unless it is duly justified to rely on other sources of clinical performance data.

5. The scientific validity data, the analytical performance data and the ***clinical performance data***, their assessment and the clinical evidence derived therefrom, ***shall be documented in the performance evaluation report*** referred to in Section 1.3.2 of Part A of Annex XIII. The performance evaluation report shall be ***part of the technical documentation***, referred to in Annex II, relating to the device concerned.

CHAPTER VI

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6. The performance evaluation and its documentation ***shall be updated throughout the life cycle of the device concerned with data obtained from implementation of the manufacturer's PMPF plan*** in accordance with Part B of Annex XIII ***and the post-market surveillance plan*** referred to in Article 79.

The performance evaluation report for ***class C and D devices shall be updated*** when necessary, but ***at least annually***, with the data referred to in the first subparagraph. The summary of safety and performance referred to in Article 29(1) shall be updated as soon as possible, where necessary.

CHAPTER VI

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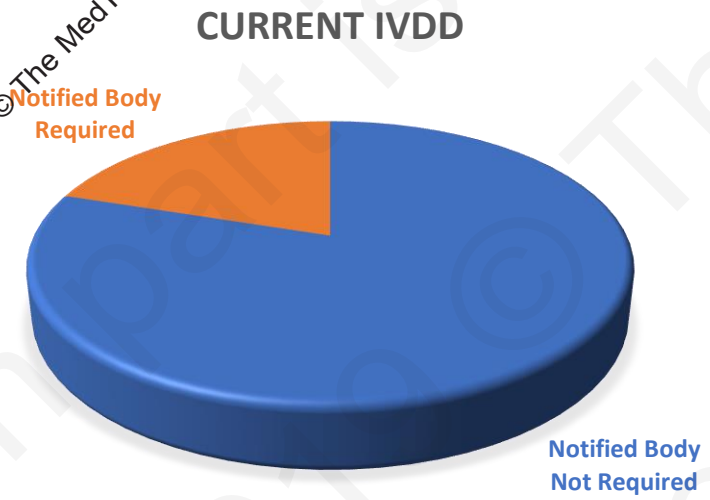
Article 56

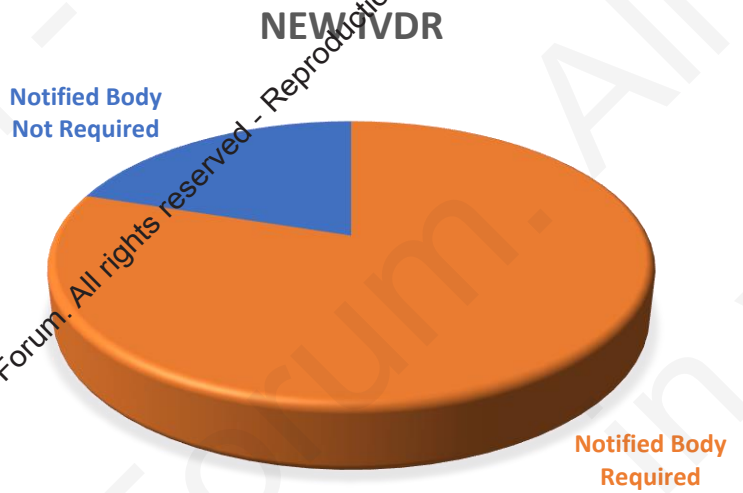
Performance evaluation and clinical evidence

7. Where necessary to ensure the uniform application of Annex XIII, the Commission may, having due regard to technical and scientific progress, adopt implementing acts to the extent necessary to resolve issues of divergent interpretation and of practical application. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3).

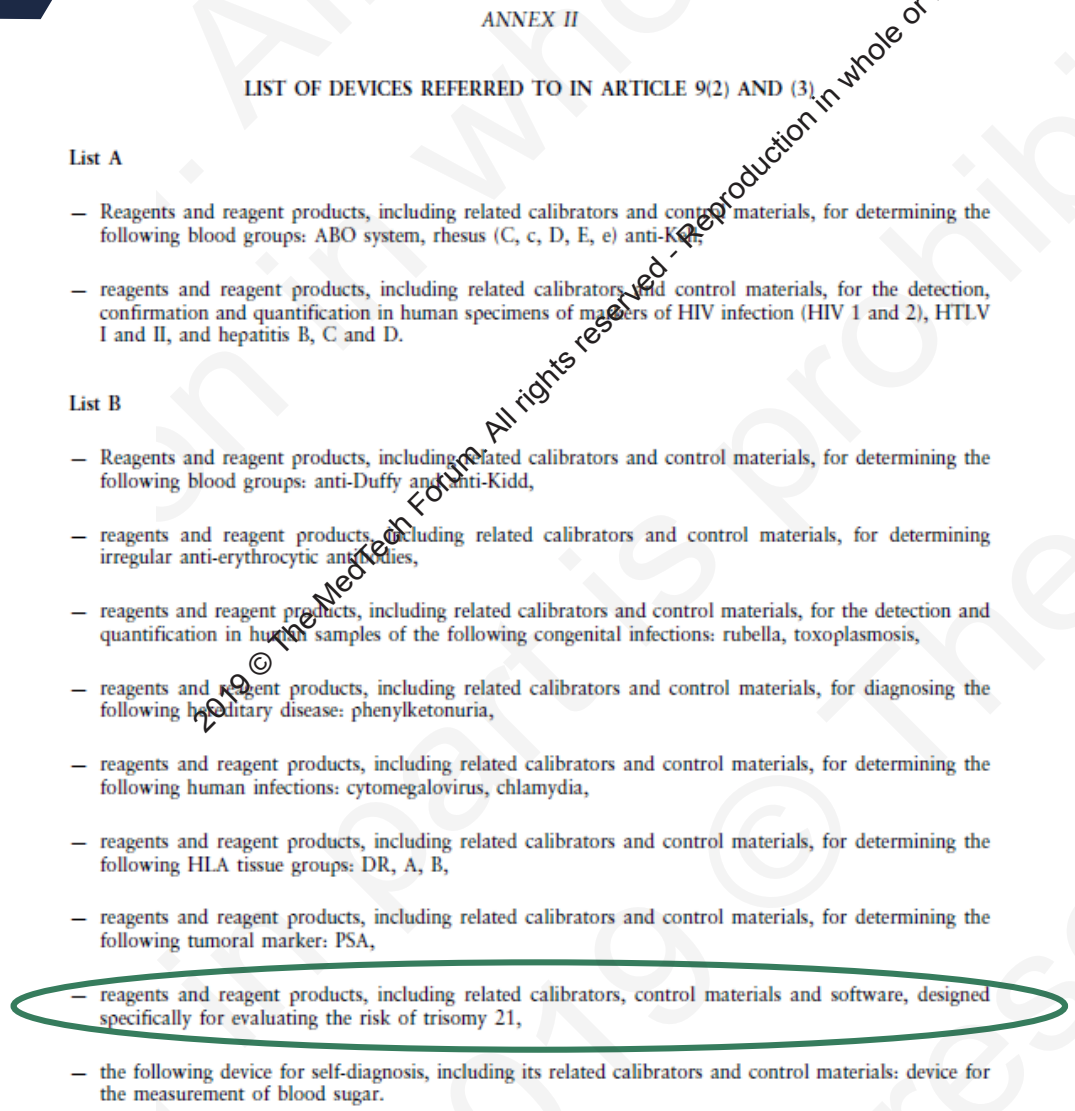
The 80:20 Inversion

Completely New system for classification
List A, List B, home use and “everything else” has gone
Risk based system using 7 classification rules (see annex VIII)





The Rapid and sometimes Dark World of IVDs



ANNEX II

LIST OF DEVICES REFERRED TO IN ARTICLE 9(2) AND (3)

List A

– Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell,

– reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.

List B

– Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd,

– reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies,

– reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis,

– reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria,

– reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia,

– reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B,

– reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA,

– reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21,

– the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.

- Technology advances with ever increasing acceleration
- IVD directive issued October 1998
- Minor (inconsequential) update September 2003
- Corrigenda Jan 1999 and Jan 2002
- T21 test is List B – requires a Notified Body
- T18 and T13 are non List A non List B – self certified
- The 80:20 inversion will remove poor quality IVDs but will also challenge good manufacturers who have never had regulatory scrutiny
- Small companies my become unintended casualties

Established Products

What data is needed to support the intended purpose ?

- Performance Evaluation Plan (See Annex XIII, Part A, Section 1.1)
- Performance Evaluation Report (See Annex XIII, Part A, Section 1.3.2); containing:
  - Scientific validity report (See Annex XIII, Part A, Section1.2.1)
  - Analytical performance report (See Annex XIII, Part A, Section1.2.2)
  - Clinical performance report (See Annex XIII, Part A, Section1.2.3)
    - ….shall achieve the performances, as stated by the manufacturer and in particular, where applicable: the clinical performance, such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations
  - Conclusions drawn from assessment of the clinical evidence (Article 56, paragraph 3 & Annex XIII 1.3.1)
- NOTE: Clinical performance studies shall be performed unless due justification is provided for relying on other sources of clinical performance data.

Established Products

Additional Requirements for specific demographics/situations

- Requirements for obtaining informed consent (See Article 59)
- Performance studies on incapacitated subjects (See Article 60)
- Performance studies on minors (See Article 61)
- Performance studies on pregnant or breastfeeding women (See Article 62)
- Performance studies in emergency situations (See Article 64)
- Interventional clinical performance studies (See Annex XIV)

Established Products

How to assess what clinical evidence data you have – is it valid?

- There is no Grandfathering!
- How up-to-date is your data?
- Does it satisfy ***all*** of the requirements per slide 11?
- If you have not performed a Clinical Performance Study, can you properly justify your position for relying on other sources of clinical performance data ?
  - Recognised Quality Assurance scheme
  - Performance against recognised standards
- Has your data ever been independently reviewed? Will it stand up to Notified Body scrutiny?

Agenda

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Generating Data – Why?

Why

There is a *requirement* to provide a body of clinical evidence that is proportional to the risk classification of the device

Generating Data – How Much?

How Much?

According to Article 56 (Performance evaluation and clinical evidence), the *manufacturer* shall *specify and justify* the level of the clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements.

How Much?

Clinical evidence requirements will be influenced by:

- The lower the risk classification = the less data required
  - The majority of devices (classes B, C and D) will require clinical evidence to demonstrate the benefits and safety of the device.
- The more established the device = the less data required
  - Novelty – avoid where possible
  - Assay technology, e.g. lateral flow immunoassay
  - Scientific/clinical recognition of the analyte of interest
- The less variability of the subject population and disease state = the less data required

Generating Data – How?

How?

Clinical Evidence

Scientific validity

Analytical performance

Clinical performance

} Performance Evaluation

How?

Types of evidence that may be submitted include:

- scientific (peer-reviewed) literature,
- consensus expert opinions/ positions from relevant professional associations,
- published experience (gained by routine diagnostic testing)
- analytical performance studies - using certified reference materials or reference measurement procedures
- clinical performance studies – device tested in parallel to routine diagnostic testing performed for patient management care

How?

To demonstrate the *scientific validity* and the *analytical and clinical performance*, Annex XIII (1.2) requires manufacturers to:

- identify through a systematic scientific literature review the *available data relevant to the device* and its intended purpose and identify any remaining unaddressed issues or gaps in the data;
- appraise all relevant data by evaluating their suitability for *establishing the safety and performance* of the device;
- generate any new or additional data necessary to address outstanding issues.

How?

NOT NOVEL DEVICES

To demonstrate the scientific validity and the analytical and clinical performance, Annex XIII (1.2) requires manufacturers to:

- identify through a systematic scientific literature review the available data relevant to the device and its intended purpose and identify any remaining unaddressed issues or gaps in the data;
- appraise all relevant data by evaluating their suitability for establishing the safety and performance of the device;
- generate any new or additional data necessary to address outstanding issues.

How?

Clinical Evidence

Scientific validity

Analytical performance

Clinical performance

} Performance Evaluation

How?

Novel devices or companion diagnostics needs to establish the association between the analyte of interest to the relevant clinical condition

How?

Clinical Evidence

Scientific validity

Analytical performance

Clinical performance

} Performance Evaluation

How?

For novel tests, it may not be possible to demonstrate trueness since recognized reference materials or a suitable comparative method are not likely to be available.

If there are no comparative methods then different approaches can be used (e.g. comparison to some other well-documented method, comparison to the composite reference method).

In the absence of such approaches, a clinical performance study comparing test performance to the current clinical standard practice would be needed.

How?

Clinical Evidence

Scientific validity

Analytical performance

Clinical performance

} Performance Evaluation

How?

Clinical performance studies must be performed, unless due justification is provided for relying on other sources of data.

How?

Challenges

- Cost
- Time to market
  - Developing clinical performance study plan, ethical review + approval
- Access to patient specimens,
  - requirements for fully informed consent
- Availability of clinical performance study sites,

How?

Left-over samples or interventional clinical performance studies

CPSP needs to provide justification for the use of left-over samples versus interventional clinical performance studies.

How?

Exception of left-over samples:

Performance studies using left-over specimens do not need Competent Authority approval. This does not apply to performance studies involving companion diagnostics using left-over samples.

Ethical review is still required for all performance studies.

How?

Exception of left-over samples:

No description of the expected risks and benefits of the device with regards to the medical procedures involved and patient management needed

How?

Exception of left-over samples:

No clinical outcomes/endpoints used need to justify or look at the potential implications for individual health and/or public health management decisions

Practical Considerations

Practical Considerations

NOW is the time to begin data collection…

Practical Considerations

Data collected on currently marketed products can be used to support the clinical evidence report.

Practical Considerations

Develop a robust and comprehensive post-market surveillance program.

Data proactively collected over the next two years, prior to applying for certification under the *IVDR*, can be included in the clinical evidence report.

Practical Considerations

<u>Post-market performance follow-up (PMPF) studies</u>

The aim to:

- confirm The safety, performance and scientific validity throughout the expected lifetime of the device, through the proactive collection of scientific data
- confirm the continued acceptability of the benefit/risk ratio
- detect emerging risks on the basis of factual evidence

Practical Considerations

Utilise PMPF studies to address minor gaps in clinical evidence. Potentially justify not carry out clinical performance study.

Practical Considerations

Usability studies vs clinical performance study

- Near-patient testing (clinical environment)
- self testing (intended user)

Pending sufficient levels of supporting clinical evidence exist

Thank you

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