

ADOPT BBMRI-ERIC Grant Agreement no. 676550

DELIVERABLE REPORT

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Executive Summary

The new In Vitro Diagnostic Device Regulation (IVDR)^{1,2} introduces significant changes for IVD manufacturers that plan to market their products in Europe. In ADOPT BBMRI-ERIC the IVDR has been analyzed in terms of its risks and opportunities and together with national experts, explored the possible implications it presents for the biobanks in Europe. Based on the analysis, biobanks face a *'window of opportunity'* due to legal obligations forced on IVD manufacturers. One of the major obligation for IVD manufacturers is to demonstrate **clinical evidence, performance evaluation and performance studies**³ in order to declare that the processes, product or service meet the relevant regulatory requirements. Hence, the manufacturers will be in need of quality samples and biobanks can provide samples with defined specifications to be used as pre-analytical controls. Consequently, biobanks could develop themselves into strategic partners for IVD manufacturers and accelerate their R&D projects.



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Background

Regulatory framework

In 2012, the Commission adopted a package of measures on innovation in health. The package consisted of a Communication and two regulation proposals to revise the existing legislation on general medical devices and in vitro diagnostic medical devices. In particular, the Directives on active implantable medical devices (90/385/EEC) and on medical devices (93/42/EEC) were **to be replaced by a Regulation** on medical devices, while the **Directive on in-vitro diagnostic medical devices (98/79/EC) was to be replaced by a Regulation on the same subject**¹. In May 2016, the European Union (EU) agreed to draft text for the In Vitro Diagnostic Device Regulation (IVDR)² that will replace the existing In Vitro Diagnostic Devices Directive (IVDD) 98/79/EC. The IVDR will enter into force starting May 2017 and the IVDR requirements must be implemented by May 2022.

Biomarkers

Access to quality defined human biological samples and associated clinical data is essential for the research, development and validation of biomarkers. To achieve the optimal utilization of large European biobanks it is important to standardize the collection procedures of samples and data. One aim of ADOPT BBMRI-ERIC is to compile the requirements of biobank quality management and standardisation in compliance with published CEN Technical Specifications (CEN/TS)⁴ for pre-examination processes respectively standardized sample handling procedures.

Modern biomarkers comprise a broad spectrum of analytes and analytical technologies (e.g., in situ techniques on tissues, such as immunohistochemistry or in situ hybridizations; analyses of isolated biomolecules, such as genomic DNA, free circulating DNA, RNA, proteins or metabolites by various omics technologies). In order to ensure reliability of analytical data generated by the various techniques, the biological samples analyzed have to meet specific quality criteria and also the analytical technologies and technology providers must fulfil necessary quality criteria. The latter is essential for the IVD manufacturers and ADOPT BBMRI-ERIC has taken the initiative to analyze the directive regarding possible implications to biobanks.

Description of work and efforts

Meetings of BBMRI-ERIC National Node representatives to discuss implications of the IVDR

After the IVDR was published in August 2016, BBMRI.fi contacted BBMRI-ERIC National Nodes to present the IVDR document and to identify national experts to join the conversation. Consequently, BBMRI.fi organized a webinar in collaboration with BBMRI-ERIC in January 20, 2017 aiming to

- present and discuss the general outline of the regulation
- identify and discuss the points to consider from the biobanks' perspective
- present and discuss the quality aspects and considerations for biobanks



The meeting concluded the following:

- Biobanks and BBMRI-ERIC together need to raise the awareness among the IVD manufacturers about the availability of human samples that meet the quality requirements of the manufacturers. European biobanks can indeed provide an ample source of pre-analytical controls for the IVD manufacturers.
- Samples prepared by different methods and with defined quality can be of great value to the IVD manufacturers and will therefore accelerate their R&D projects for the benefit of healthcare;
- Biobanks should be informed about the ‘window of opportunity’ to develop themselves into strategic partners for IVD manufacturers together with BBMRI-ERIC Expert Centres.
- ADOPT-BBMRI-ERIC project can help the IVD manufacturers to focus their attention to those biobanks that meet the requirements of IVDR .

BBMRI-ERIC Self-Assessment Survey (WP6 D6.3) will support BBMRI-ERIC biobanks to assess their procedures and sample specifications to demonstrate that their compliance with CEN Technical Specifications for pre-examination processes potentially required by IVD manufacturers.

- The implications of the IVDR have also been widely discussed in the BBMRI-ERIC Management Committee meetings in 2016-2017. The issues still open are: 1) should the sample donors be informed in case their samples are being used as pre-analytical controls for applied research purposes, and 2) is there a need for biobanks to start collecting samples for this purpose in the future. BBMRI-ERIC has a unique position to tackle these points with its stakeholders: patient organizations and industry representatives

Schedule

The implications of IVDR to biobanks are centrally related to sample quality because the manufacturers will be in need of quality samples in the future. The biobanks can use this opportunity to provide samples with defined specifications for the manufacturers. The publication of the IVDR was delayed until August 2016 due to the publishing timetable of the IVDR. Consequently, the current ADOPT D6.1 will describe initial implications of the IVDR. There will be a need to follow the execution of the IVDR starting from May 2017 and we anticipate that during 2017 the implications of the IVDR to biobanks can be discussed during the Global Biobank Week (September 2017) and later during the BBMRI-ERIC Stakeholder Forum (planned in the Oct-Nov 2017) specifically organized for industrial stakeholders



Results – Guidelines to Biobanks

Important definitions in relation to the IVDR

- **What is a IVD:**
In vitro diagnostics are tests that can detect disease, conditions, or infections. Some tests are used in laboratory or other health professional settings, and other tests are for consumers to use at home
- **Companion Diagnostics:**
A companion diagnostic is a medical device, often in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional to determine whether benefits of a product to patients will outweigh any potential serious side effects or risks.
- **Laboratory Developed Tests:**
A laboratory developed test is a type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory
LTDs can be used to measure or detect a wide variety of analytes (substances such as proteins, compounds like glucose or cholesterol or DNA) **in a sample taken from a human body.**
- **Tests used in Clinical Care:**
Laboratory tests are medical devices that are intended for **use on samples of blood, urine, or other tissues or substances taken from the body** to help diagnose disease or other conditions.
- **Home use Tests, Blood glucose monitoring devices etc**

What is the IVDR

- **The new IVDR proposal to the European parliament is a near 400 pages long document, including 10 Chapters, 90 Articles and 15 Annexes ⁵**
- **The IVDR contains key changes, including:**
 - Definition of an IVD is expanded
 - Now includes also genetic tests, tests used to predict treatment response and software
 - A risk-based IVD classification system required
 - Four new classes (lowest risk to highest risk)
 - Identification, traceability and improved access to information.



- Manufacturers required to use a UDI (Unique Device Identification)
 - Increase of post-market surveillance and reporting
 - Requirements for risk-based clinical evidence and protection of patient safety in clinical performance studies
 - Increased clinical evidence required to demonstrate conformity with the general safety and performance requirements
 - Requires designated responsibility for regulatory compliance
 - Manufacturers need to have a responsible person for regulatory compliance
- **Biobanking related Standards and regulations in the IVDR**
 - **IVDR Chapter V: Classification and conformity assessment and IVDR Chapter VI: Clinical evidence, performance evaluation and performance studies**
 - Conformity assessment or compliance assessment determines directly or indirectly that a process, product or service meets relevant technical standards and fulfills relevant requirements
 - IVD manufacturers have to show conformity that the product (device, kit, lab) they are manufacturing and releasing to the market meet the regulatory requirements
 - **IVDR Annex II: Technical Documentation – Product verification and validation:**
 - The documentation shall contain the results of verification and validation testing and/or studies undertaken to demonstrate conformity of the device with the requirements of this Regulation and in particular the applicable general safety and performance requirements. This includes:
 - Information of analytical performance
 - Specimen type: This section shall describe the different specimen types that can be used, including their stability and storage conditions**
 - **How can biobanks comply with quality**
 - BBMRI-ERIC Partner Charter encourages biobanks to implement quality management⁶
 - BBMRI-ERIC will organize a self-evaluation of biobanks during spring 2017⁶
 - Implementation of international ISO and CEN/TS applicable for biobanks⁴
 - The ADOPT BBMRI-ERIC IT tool and Self-Assessment Survey⁷ (D6.2) supports the structured monitoring respectively the assessment of the pre-analytical process of samples as defined in the CEN/TS. This tool also provides key data for monitoring interoperability and quality of biobanks and appropriate collections.



- **The IVDR will offer biobanks a possibility to offer samples as pre-analytical controls for manufacturers**
 - Implementation of IVDR will create a need for control samples of defined quality
 - Samples from one donor prepared by different methods will be of great value for validation studies

Next Steps

- Increase awareness of IVDR among biobanks
 - Based on the current ADOPT Deliverable document, publish a guideline for biobanks in BBMRI-ERIC Newsletter
- Increase awareness of manufacturers
 - Organise an IVDR discussion / presentation at the BBMRI-ERIC Stakeholder Forum (end 2017 – beg. 2018)
- BBMRI-ERIC Self-Assessment surveys support biobanks to demonstrate compliance to CEN/TS for pre-examination processes
 - BBMRI-ERIC aims to publish CEN/TS compliance of biobanks in 2017

News

EU Parliament Adopts New Medical Device, IVD Regulations⁸

Now that the legislative process has concluded, the Medical Device Regulations (MDR) and In Vitro Diagnostics Regulations (IVDR) are set to be formally published in the Official Journal of the European Union in May 2017.

European Parliament: Medical devices: more safety, more traceability⁹

References and useful links

¹European Commission - <http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision/>

²IVDR - http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision_en

³Part II – Annex 2 addresses specific issues relevant for IVDs - http://eur-lex.europa.eu/resource.html?uri=cellar:487acc33-213b-4fdf-bdbb8840209a8807.0001.04/DOC_3&format=PDF

⁴European Committee for Standardisation - cen.eu

⁵Proposal for a Regulation of the EUROPEAN parliament and of the Council on in vitro diagnostic medical device - <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012PC0541&from=EN>



⁶BBMRI-ERIC Quality Policy - <http://www.bbMRI-eric.eu/services/standardisation/>

⁷BBMRI-ERIC Quality Management - <http://www.bbMRI-eric.eu/BBMRI-ERIC/quality-management/>

⁸EU Parliament Adopts New Medical Device, IVD Regulations - <http://raps.org/Regulatory-Focus/News/2017/04/05/27279/EU-Parliament-Adopts-New-Medical-Device-IVD-Regulations/>

⁹European Parliament: Medical devices: more safety, more traceability; Press release - <http://www.europarl.europa.eu/news/en/news-room/20170329IPR69055/medical-devices-more-safety-more-traceability>



Appendix I

ADOPT BBMRI-ERIC (WP6) IVD Regulation Webinar 20 January 2017 @ 13:00-14:00 – Agenda and Summary

How will the IVD regulation affect biobanks?

Participants: Anne Cambon-Thomsen, Annelies Debucquoy, Annemarie Marold, Anu Jalanko, Berthold Huppertz, Cornelia Stumptner, Esther Zammit, Iiro Hamalainen, Jasper Bovenberg, Kinga Wilkus, Kirsting Goldring, Laurent Dolle, Laurenz Goverts, Loreana Norlin, Malcom Pace, Manuela Locatelli, Maria Grazia Daidone, Michaela Mayrhofer, Michael Hummel, Kurt Zatloukal, Mieke de Wilde, Morten Oien, Olga Tzortzatou, Sabine Bavamian, Sabrina Neururer, Sara Casati, Sofiane Necia

AGENDA

1) Introduction to the topic

- I. General outline of the IVD-Regulation and the ADOPT Task
Anu Jalanko/BBMRI.fi
- II. Points to consider from the Biobank perspective
Kurt Zatloukal/BBMRI.at
- III. Quality aspects and considerations for biobanks
Andrea Wütte/BBMRI-ERIC

2) Discussion topics

- I. Is it necessary to collect viewpoints / statements separately from National Nodes?
- II. Requirements of sampling: What standards should biobanks follow?
- III. The format of ADOPT Task Report

Webinar summary

- The IVDR will offer biobanks a possibility to offer samples as pre-analytical controls for manufacturers
 - Implementation of IVDR will create a need for control samples of defined quality
 - Samples from one donor prepared by different methods will be of great value for validation studies
- The awareness within the BBMRI-ERIC biobanks about the possibilities of the IVDR should be increased
- BBMRI-ERIC should find ways to increase the awareness and promote the IVDR and its possibilities to the manufacturers
- BBMRI-ERIC Self-Assessment Survey preparations should be sped up so that BBMRI-ERIC biobanks would soon be able to offer CEN/TS compliant samples

Action point: ADOPT WP6 Task leaders (Anu Jalanko & Kurt Zatloukal) together with Andrea Wutte shall prepare a proposition to the MC of BBMRI-ERIC of the next steps. This will be presented in during the next ADOPT/MC meeting 7-8.3.2017

