In vitro diagnostics BIC Regulatory Guide

Overview of regulatory and authorisation challenges and transnational exchanges of clinical data and samples

Myszczynski, Pawel ; Daussin, Valérie; Kuldo, Joanna; Piwowarczyk, Katarzyna

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BIOMARKER COMMERCIALIZATION

In vitro diagnostics

BIC Regulatory Guide

Lead author: **Paweł Myszczyński**

Contributing authors: **Valerie Daussin, Joanna Kułdo, Katarzyna Piwowarczyk**

Reviewer: **Jens Pfannkuche**

AALBORG UNIVERSITY HOSPITAL

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The guide has been prepared by the EU-project Biomarker Commercialization (BIC). The project is comprised of 8 partners in the Baltic Sea Region (BSR) united by the same challenges, as well as a common objective of more efficiently introducing new and improved IVD-applicable biomarkers from discovery to clinical use. The project's budget is EUR 2.55 million and is co-financed by the European Regional Development Fund through the Interreg Baltic Sea Region Programme with EUR 1.96 million.

Interreg
Baltic Sea Region

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

Lead Partner:
Ideklinikken –
Aalborg University Hospital
The Northern Denmark Region
Hobrovej 18-22
9100 Aalborg
Denmark

Authors:
Paweł Myszczyński, Wroclaw Technology Park S.A.
Joanna Kułdo, Wroclaw Technology Park S.A.
Katarzyna Piwowarczyk, Wroclaw Technology Park S.A.
Valerie Daussin, Aalborg University Hospital

Reviewer:
Jens Pfannkuche, Ph.D.

Editorial design:
Kamila Dankowska, Katarzyna Placek
This Way Design

With the contribution of the entire BIC consortium:
BioCon Valley® GmbH, Germany
—
Biopeople, University of Copenhagen, Denmark
—
Ideklinikken, Aalborg University Hospital, Denmark
—
Tartu Biotechnology Park OÜ, Estonia
—
Turku Science Park Oy, Finland
—
University of Turku, Finland
—
Vilnius University, Lithuania
—
Wroclaw Technology Park SA, Poland

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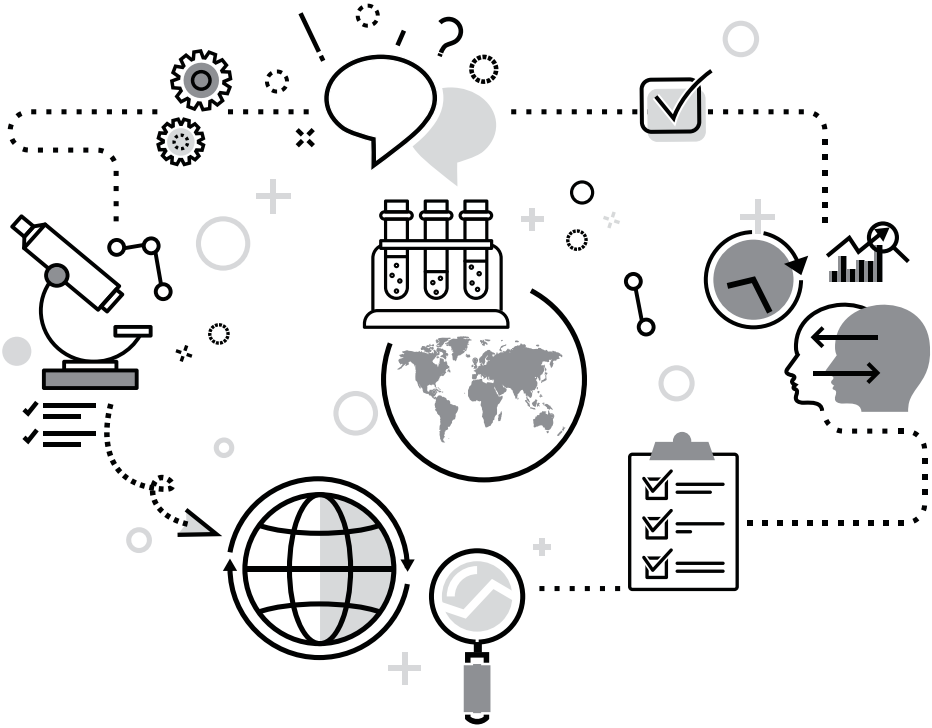
INTRODUCTION



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The objective of the document:

"In vitro diagnostics BIC Regulatory Guide" was created to extend, organise, and systematise expertise of regulatory affairs concerning stakeholders in the value chain of biomarker commercialization, who participate in the process of introducing *in vitro* diagnostic (IVD) medical devices, especially IVD-applicable biomarkers to the market. Regulatory requirements and restrictions play a crucial role in IVD biomarker assay development. With the introduction of new European regulations (from IVD medical device directive to IVD medical device regulation), there is some regulatory uncertainty and currently no interpretation available. The uncertainty encompasses mainly operability of EUDAMED database and UDI system, as well as availability of notified bodies, harmonized standards and common specifications for IVD device that face stricter pre-market control for up-classification into higher risk IVD medical devices. It should be stated very clearly that this guide is applicable for in vitro diagnostics (IVD) for clinical use in humans.

This guide is one of the tools developed by the BIC (Biomarker Commercialization) project and was narrowed down to the IVD field, which was decided by the project consortium. The BIC tools focus on the early stages of development (stages from 1 to 5 as outlined in this RG, figure 6) and assist biomarker discoveries in reaching their full market potential as an IVD medical device (at September 2020 it is confirmed that last 2 phases of commercialization will be a subject of continuation project). However, by the way of exception and because of the coherency issue, the BIC Regulatory Guide covers all stages of commercialization (regulatory affairs exist throughout the entire lifecycle of the IVD medical device). In order to place a biomarker product as an IVD medical device on the market successfully, entrepreneurs, as well as researchers, should be acquainted with the relevant regulations. This guide contains information about mandatory regulatory requirements, as well as tips and good practices, which are essential, especially at the beginning of the commercialization process. Due to the fact that regulatory issues (closely related to the commercialization of biomarkers) do not directly affect all interested parties, this document aims not only at elaboration of on regulatory affairs, but also provides guidance on how to improve cooperation between relevant stakeholders. The organisation of work under the expectations of other relevant stakeholders is crucial for a beneficial and effective launch of the final product on to the market. It is very important to emphasize that the overall rule of **meeting the regulatory requirements is the responsibility of the manufacturer.**

BASIS OF THE DOCUMENT:

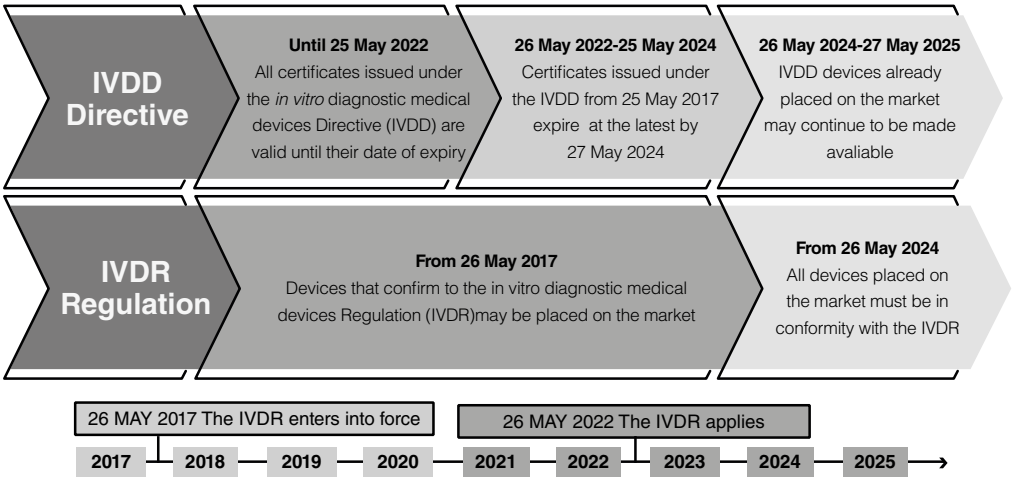
Regulatory issues in the IVD biomarker commercialization field have been introduced in respect to the commercialization model proposed by the BIC consortium. The substantive content was based on Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices ('IVDR'). However, in order to maintain document transparency, comprehensiveness and for the reader's needs, some of the content is a compilation of output from BIC project activities and conclusions, which are based on IVDR analysis and interviews conducted by BIC partners, as well as suggestions from the project Advisory Board.

ADDITIONAL INFORMATION:

In order to gain the most comprehensive knowledge, this document should be read in conjunction with other tools developed by the BIC consortium and additionally with IVDR.

Every reference in this document is related to Regulation (EU) 2017/746 of the European Parliament and of the Council on *in vitro* diagnostic medical devices, unless the context of a statement indicates otherwise. **Regulation 2017/746 on IVDs shall apply from 26 May 2022, however, by way of derogation some articles of Regulation are applicable prior or after this date (details can be founded in article 113 of IVDR and transitional provisions in the IVD field can be found in article 110).**

Figure 1: Transition timelines from the IVDD to the IVDR



For project purposes and in respect to the commercialization value chain determined by BIC consortium, specific terminology is used. Definitions in this document reflect the EU IVDR terminology, FDA terminology and other specific terminology indicated by the BIC glossary.

However, in order to simplify the understanding or to compress the content, the novel terms concerning regulatory issues are introduced directly into this document. The novel terms created for the purpose of this document, that do not correspond with official terminology, can be found in sub-chapter 1.1 Definitions & acronyms (section "Novel terms").

LEGAL NOTE:

Only European legislation that is available online

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELE:02017R0746-20170505

in the Official Journal of the European Union can be considered authentic. The information and views contained in this manual are those of the author and do not represent the official opinion of the European Communities or of EU Member States. Despite careful processing, all information in this work is provided without guarantee; liability on the part of the author or the publisher is excluded.

It is therefore essential to study the original legal texts; it is often advisable to consult the competent authorities or the European Commission when in doubt. The legally binding interpretation of the EU legal texts is reserved to the European Court of Justice.

Should this manual contain links to third-party websites, the author accepts no liability for their contents, as he does not adopt them as his own, but merely refers to their status at the time of initial publication.

The transfer and the use of personal data, in the case of the use/transfer of biological material, during biomarker development against the background of the commercialization value chain presented in this document, shall respect the EU regulations regarding personal data protection: Regulation (EU) 2016/679 and Regulation (EC) No 45/2001.

This guidance considers merely EU regulatory framework on in vitro diagnostic medical devices (see definition below), any affairs that the Regulation does not encompass, where applicable, national regulations may apply.

1.1 Definitions & acronyms

IVDR TERMINOLOGY:

COMPANION DIAGNOSTIC – a medical device which is essential for the safe and effective use of a corresponding medicinal product to:

- **a.** identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
- **b.** identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;

CONFORMITY ASSESSMENT – the process demonstrating whether the requirements of the EU IVDR relating to a device has been fulfilled before placing the product on the market and usually conducted by a notified body;

CS – Common Specifications;

DEVICE FOR NEAR-PATIENT TESTING – any device that is not intended for self-testing, but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional with limited training;

DEVICE FOR PERFORMANCE STUDY – a device intended by the manufacturer to be used in a performance study;

DEVICE FOR SELF-TESTING – any device intended by the manufacturer to be used by lay persons, including devices used for testing services offered to lay persons by means of informational society services;

EUDAMED – European database on medical devices;

GSPR(S) – General Safety & Performance Requirements;

IVDR – In Vitro Diagnostic Regulation; REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU;

IN VITRO DIAGNOSTIC MEDICAL DEVICE means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- **a.** concerning a physiological or pathological process or state;
- **b.** concerning congenital physical or mental impairments;
- **c.** concerning the predisposition to a medical condition or a disease;
- **d.** to determine the safety and compatibility with potential recipients;
- **e.** to predict treatment response or reactions;
- **f.** to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices.

MDCG – Medical Device Coordination Group;

NOTIFIED BODY – means a conformity assessment body designated in accordance with the IVDR;

PERFORMANCE EVALUATION – an assessment and analysis of data to establish or verify the scientific validity, the analytical and, where applicable, the clinical performance of a device;

PERFORMANCE STUDY – a study undertaken to establish or confirm the analytical or clinical performance of a device;

PMPF STUDIES – Post-Market Performance Follow-Up studies;

PMS – post-market surveillance

PMS PLAN – post-market surveillance plan

PRRC – Person Responsible for Regulatory Compliance

PSUR – Periodic Safety Update Report;

SRN – Single Registration Number;

TD – technical documentation (Annex II of IVDR) + technical documentation after placing a product on the market (Annex III of IVDR)

UDI SYSTEM – Unique Device Identification system.

OTHER TERMINOLOGY:

BBMRI-ERIC – Biobanking and Biomolecular Resources Research Infrastructure ERIC;

BIC GUIDE – the commercialization tool collection on IVD biomarker assay development, developed within the BIC project;

BIOMARKER – a characteristic that can be objectively measured and evaluated as an indicator of a physiological or pathological process in an individual or an individual's response to a therapeutic intervention. The closest synonym to a clinically useful biomarker in the context of in vitro diagnostics (IVD) is an analyte, i.e., a component (molecule) in a clinical sample. Its presence, absence or concentration is measured in an analytical procedure, e.g. by a laboratory test, to obtain information on an individual's health status.

The biomarker (or analyte) can, for example be a nucleic acid, protein, polysaccharide or metabolite. Alterations found, e.g. by clinical inspection, physical measurement of organ functions (e.g. blood pressure, cardiogram), or microscopy of visual tissue appearance are not included in the scope of the current guide. The scope is also narrowed down to human applications although many characteristics and requirements are similar to veterinary applications.

BSR – Baltic Sea Region;

CAMD – Competent Authorities for Medical Devices;

CLIA – Clinical Laboratory Improvement Amendment of 1988;

CRO – Contract Research Organization – an organization that supports by conducting performance studies on commission;

EAAR – European Association of Authorised Representatives;

ECONOMIC OPERATOR – as defined in article 2 (28) of IVDR

FAIR – The FAIR Guiding Principles for scientific data management and stewardship

FD&C – Federal Food, Drug, and Cosmetic Act;

FTO – Freedom to Operate – an analysis determining that particular action, such as testing or commercializing a product, can be done without infringing on valid intellectual property rights of others;

GDPR – REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC ("General Data Protection Regulation");

GLP – Good Laboratory Practice

ISBER – International Society of Biological and Environmental Repositories;

IMDRF – International Medical Device Regulators Forum

KOL(S) – Key Opinion Leader(s);

MEDICAL DEVICE or **DEVICE** means biomarker IVD assay in this document;

MTA – Material Transfer Agreement;

POC – Proof of Concept

QPBR – Quality Practices in Basic Research

RESEARCHER – in the meaning of academic researcher

SOP – Standard Operating Procedure – a set of instructions for routine operations (often implemented by GxP);

STAKEHOLDER – a member of the biomarker commercialization value chain;

TRL ANALYSIS – Technology Readiness Level – one of the assessment tools of the maturity level of a technology used by TTO's;

TTO – Technology Transfer Offices;

QMS – Quality Management System.

NOVEL TERMS & ABBREVIATIONS:

BCVC – Biomarker Commercialization Value Chain. The term was created for regulatory overview purposes;

INVESTOR – a member of the commercialization value chain who invests resources (usually money) for biomarker development;

RG – Regulatory Guide;

SPONSOR – any individual, company, institution or organisation, that takes responsibility for the initiation, management and setting up financing of the performance study. In the commercialization model established by the BIC consortium this role is generally assigned to a enterprise.

EXPLANATION:

ENTERPRISE/ENTREPRENEUR/MANUFACTURER/SME/COMPANY/ – all of these terms concern an entity, that introduces an IVD biomarker product on the market.

In vitro diagnostics BIC Regulatory Guide/Regulatory Guide /RG terms and abbreviations applied interchangeably in context of this document.

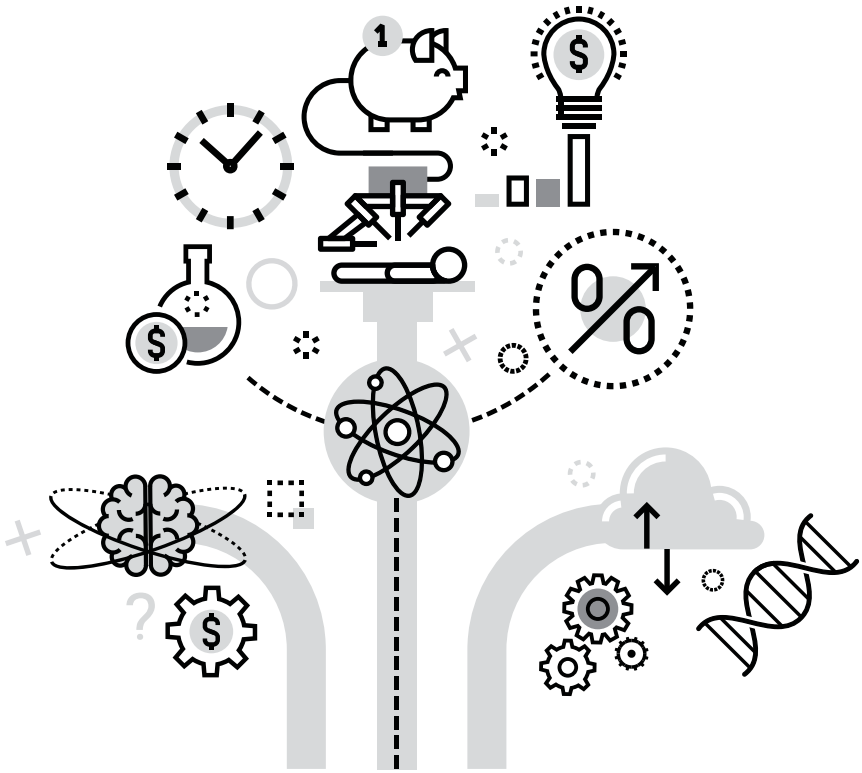
Sponsor, as an entity mentioned in the regulation, who is responsible for a performance study and its evaluation, has to be integrated into the model adopted by the project. Therefore, the role of a sponsor can be assigned to: enterprise, investor or another organisation/institution (e.g. hospital) who takes responsibility for performance studies in the relevant biomarker development project. In an ideal model of commercialization, which is the framework for all BIC activities, a sponsor is usually an enterprise from the SME sector (when an investor participates in the process as a financial resource donor) or a large enterprise itself. The role of an investor

usually remains solely as a resource provider and does not take responsibility for the performance study.

For the purpose of this document we assigned the role of sponsor to an enterprise (the most common model), which is described in sub-chapter 4.2.2 'Performance study and performance evaluation'.

2

GENERAL INFORMATION & SCHEMES



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2.1 General involvement of stakeholders in the biomarker commercialization value chain

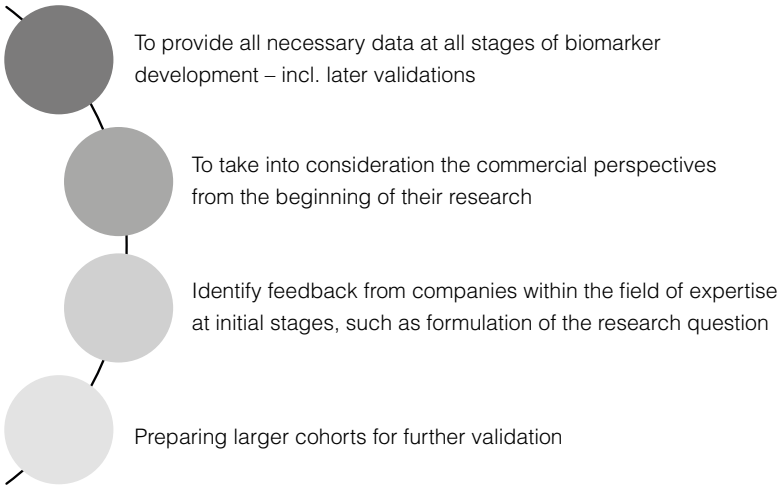
The commitment and cooperation of BCVC stakeholders is necessary for the successful completion of the process. Understanding the dependencies between particular stakeholders and their impact on various stages of the commercialization process is crucial.

One should be aware of the fact, that there are many possible **pathways of commercialization**. One path could emphasise the role of a relevant stakeholder, while another path would not be able to forecast similar stakeholder participation. The Regulatory Guide is not focused on the elaboration of all models, but is based on the currently recognised path (participation of TTOs in the process).

The "TTO model" of commercialization forecasts close collaboration between researcher and **TTO**, in order to achieve an efficient technology transfer to industry. TTOs serve as a catalyst for commercialization processes and assist in the comprehensive project evaluation. Proper cooperation with TTOs should lead to **an investor/ industrial partner** engagement or a company launch (e.g. spin-out). Collaboration with TTOs require developmental and commercial preparatory work (fig. 2).

TTO'S EXPECTATIONS OF THE RESEARCHER:

Figure 2: TTOs expectations



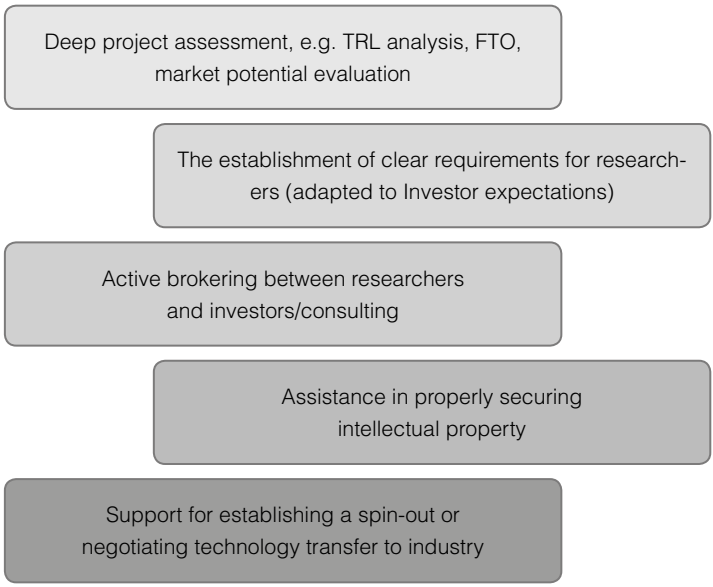
Sources: BIC interviews

TTO CHARACTERIZATION

TTOs operate based on national law and internal regulations, and each submission of invention comprising biomarker is evaluated individually. TTOs have many tools to evaluate an invention, its application, market potential, commercialization opportunities, patent strength (FTO) or the chances of finding an investor. One of the current tools used to perform this evaluation is to establish technological readiness (TRL analysis), which is a maturity indicator of the project.

BIC interviews do not provide any information on biomarker focused TTOs (within the BSR), therefore demonstrating TTO principles for managing biomarker projects seems to be important here.

Figure 3: TTO principles for biomarker projects



Sources: BIC interviews

From the TTO perspective, it would be a great facilitation if the guidelines applied in daily routine encompassed requirements for applications regarding the biomarker field, including regulatory affairs. Nowadays, TTOs base their process on the general experience of employees and good practices obtained from prior cooperation with

business representatives. According to the information gathered within the project, such **guidelines** in the biomarker sector **do not exist**, although the profiling of requirements would significantly improve the technology transfer from research to industry (e.g. TRL levels sufficient to interest an investor, PoC requirements for the biomarker field, overview of frequent industry expectations, etc.). The BIC project also aims to provide a selection tool for biomarker projects, as one of the project results (BIC Review Tool, available at bicguide.biomarker.nu).

2.2 Information on investors

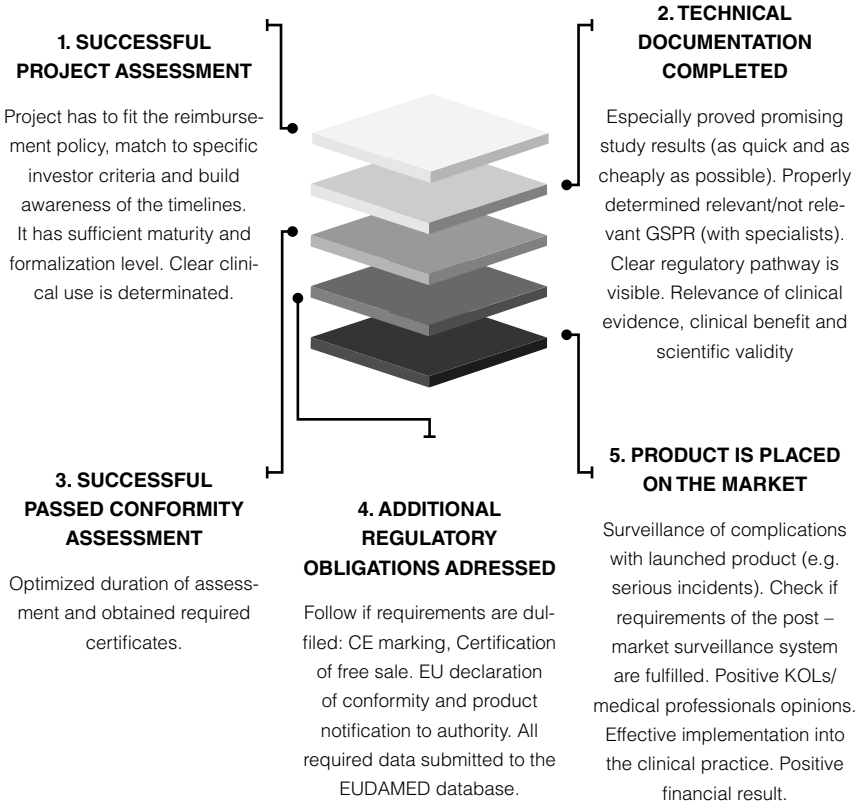
Investors usually remain solely as resource donors, mostly interested in commercial value of final product and clinical benefit associated with it rather then in scientific value of it (business approach). As resource providers, **they do not face regulatory issues themselves**. The EU IVDR is not applicable to investors. Particular attention should also be paid to the distinction between "investor" and "sponsor". A sponsor is a legally well-defined entity, which takes responsibility for the whole study (for more information look at sub-chapter 4.2.2.1 of this Guide), while investor is a general term applied to a resources provider.

However, in case of BCVC, investors can participate in a broader range of activities, e.g. providing infrastructure or expertise and participating that way in the commercialization process. Also, a possible scenario that could be taken into account, there are manufacturers acting as investors – and that way, investor equals manufacturer with all the responsibilities as outlined in article 10. Another particular situation occurs when the commercialization process is financed or co-financed by public funding. In this scenario, the entity receiving financing is responsible for the whole study, therefore becoming the sponsor. To sum up this section, there are a couple of relationships possible between the concepts of investor, manufacturer and sponsor, and each situation should be analysed individually to determine the exact scope of responsibility of each entity involved.

Output provided by project activities indicate that investors have a general knowledge about the commercialization process, as a whole. They usually have their own techniques of evaluation of a project and critical components to focus on. Usually investors are not interested in investing when a project is in such early stage of development that intended use is not already specified. Furthermore, investing in early-stage project would imply bearing the high costs related to intellectual property, technical & clinical developmental, regulatory and reimbursement costs and risks). Investors expect a clear vision of how a biomarker product fits into clinical practice and what clinical situation the biomarker assay is going to solve.

To be able to track and control the development process of a biomarker product that investors are already invested in, proposed milestones are introduced, such as the scheme below (fig. 4). This chapter aims to show what regulatory milestones of biomarker development Investors can track, in order to make an investment decision, maintain investment or exit the project.

Figure 4: Proposed milestones for investors to track during biomarker development:



This is a proposed model of milestones Investors should observe carefully during the biomarker development and investment process. The establishment of milestones to the relevant process depends on the developmental stage at which an investor has decided to invest in – it can be extended or reduced in comparison to the model presented above.

2.3 Information on biobanks and on the use of biological samples

Biobanks provide services of transferring samples and related data in the BCVC under material transfer agreements. **Biobanks**, as service providers, **do not meet IVDR requirements directly.**

Output provided by the project activities indicates, that biobanks do not consider the issue of data/sample exchange as a challenge. Many biobanks collaborate with each other within the **BBMRI-ERIC** network-biobanking initiative instituted in 2013, which has an international, as well as, a national sphere of activity. They work with standards in order to provide high quality data/samples, e.g. for research or clinical purposes. Another well-known biobanking network is **ISBER**.

However, the situation regarding the use of biological sample material, as well as biobanks themselves, is not clear. Currently, the dedicated regulation/European legal framework for the use of biological material and biobanking **does not exist** (currently draft laws are being developed in some countries) and national regulations may vary from country to country. Thus, analysis of the legal basis for the operation of biobanks is impeded, and should be interpreted through the entire legal system (at the national level) and through international law (including "soft law", e.g. Declaration of Helsinki).

In the context of protecting personal data, biobanks operate in compliance with GDPR and, because of the specific character of obtaining/using samples, also comply with relevant national regulations. Biobanks are responsible for obtaining relevant consent (e.g. patient consent) for processing personal data. When a biobank, on the basis of MTA, transfers data to an entity, that is conducting its own research, the obligations of data processing are transferred together with the subject of transfer.

2.4 Information on end-users (Hospitals/Clinicians/other End-Users)

In regards to the different models of medical services (e.g. structure, ownership) and reimbursement policy which differ from country to country, as well as a diverse concentration of regulatory issues in the field, this document does not show a unified path of biomarker assay implementation to end-user use and it is not the main goal of this project. **IVDR does not refer to the end-users.** This sub-chapter includes solely basic information about end-users.

KEY OPINION LEADERS

The strategy for end-users should play a significant role during market planning, especially a strategy for KOLs in the field. KOLs strongly influence the choices made by the other end-users. The strategy development should take place quite early in the process and relationship development with the KOL group is often outsourced.

Principles to keep in mind when developing relationships with KOL:

- identify KOLs using a scientific approach;
- clearly outline the needs of the KOL and your company;
- keep track of KOL engagement with your company;
- remember that collaboration with KOLs is a two-way street that may involve the sharing of sensitive data;
- measure and monitor the KOL relationship.

TYPES OF END-USERS

There are 3 types of end-users that have been identified by the consortium in BCVC:

1. **RESEARCH END-USERS** – this biomarker is used for internal research purposes (e.g. Bayer). Bayer uses biomarkers to guide their research to answer research questions around substances under investigation. Since the biomarker is used for internal research purposes, the CE-mark or other certification is not necessary. However, quality is of high importance and is checked according to internal guidelines.
2. **LABORATORY END-USERS** – for this type of end-user there are important factors, such as turn-around time, instrumentation needed, hands-on-time, logistics of samples and specimen types.
3. **CLINICAL END-USERS** – the most important factors in the clinic are optimal specificity, sensitivity and a clear benefit when compared to standard of practice. The Biomarker test also has to be better than the other available methods in order to be accepted. The price should relate to the add value provided.

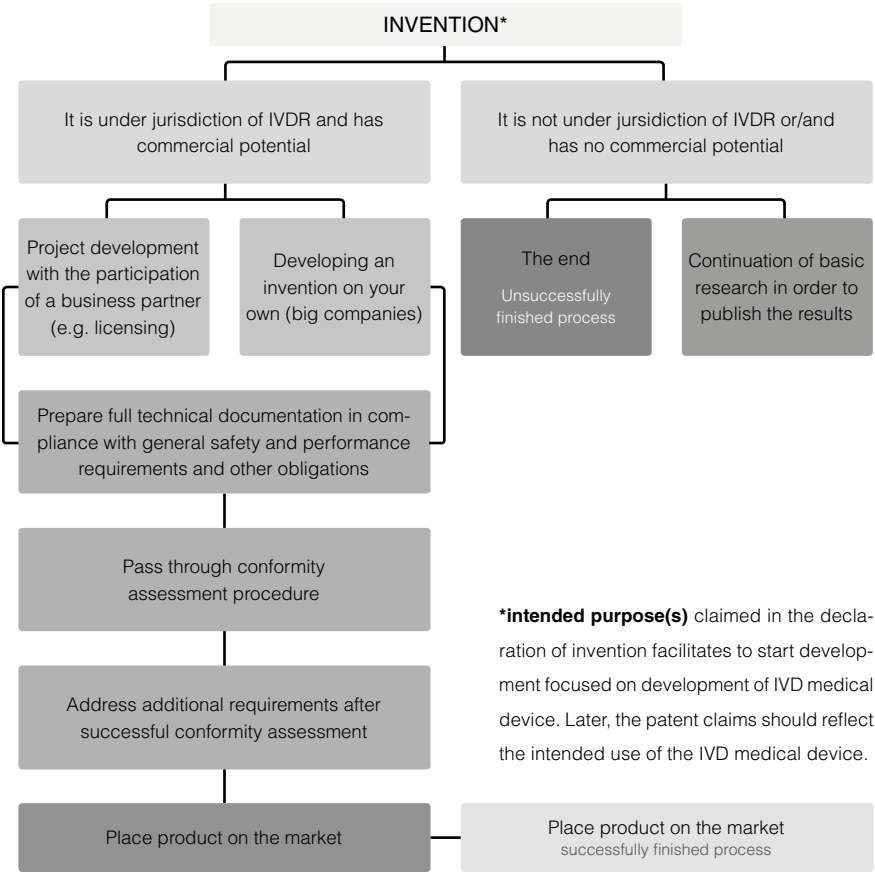
Regulation is designed to ensure the safety of the end-user and patient. Only the intended use of the device as specified by the manufacturer determines the end-user, e.g. near-patient testing device – clinical end-user. End-users should also be enabled to report serious incidents at a national level (details on incidence reporting within EUDAMED are currently not available).

IVDR QUOTE:

Healthcare professionals, users and patients should be encouraged and enabled to report suspected serious incidents at a national level using harmonised formats.

2.5 Biomarker commercialization process – general regulatory process

Figure 5: Biomarker assay commercialization process from regulatory point of view (on the basis of IVDR) – from invention to the market implementation – general scheme



***intended purpose(s)** claimed in the declaration of invention facilitates to start development focused on development of IVD medical device. Later, the patent claims should reflect the intended use of the IVD medical device.

3

COMMERCIALIZATION IN PROCESS APPROACH

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In respect to the BIC consortium decision, the project tools and other project documents (e.g. Regulatory Guide) have been developed with a commercialization process approach, according to proposed stages of commercialization. Regulatory affairs (within Regulatory Guide) are one of the aspects of commercialization the BIC project is going to cover.

Figure 6: Stages of the commercialization process of an IVD biomarker applicable product proposed by the BIC consortium

PHASE 1:
Biomarker Discovery
TRL-1 Basic principles observed

PHASE 2:
Biomarker verification and preliminary scientific validity studies
TRL-2 Proof-of-Principle studies

PHASE 3:
Development of a specific biomarker assay (prototype)
TRL-3 Proof-of-Concept assay established

PHASE 4:
Clinical performance of the prototype in laboratory settings
TRL-4 Proof-of-Concept studies with prototype assay

PHASE 5:
Pre-industrial maturation phase
TRL-5: Configuration to industrial application (Beta Prototype)
TRL-6: Technology demonstrated in a relevant environment

PHASE 6:
Industrial Assay Development
TRL-7 Clinical Validation of IVD assay

IVD

PHASE 7:
Commercial Launch and clinical implementation
TRL-8 Commercial launch of IVD assay
TRL-9 Post Launch monitoring of IVD assay

Sources: BIC project

IVDR requirements (tasks) were introduced as separate relevant stages of commercialization and in respect to the involvement of individual stakeholders. Each stage of commercialization is described (from regulatory perspective) in separate sub-chapters (from 3.1 to 3.7). Stages of commercialization that do not forecast enterprise participation in the process (early stages of development) do not contain mandatory regulatory tasks. Researchers are not legally responsible for fulfilling regulatory obligations of the IVDR.

A researcher, who is responsible for the early stages of development, will be guided to take into account a regulatory pathway that a final IVD-medical device will have to go through. Therefore, chapters regarding the early stages of development were developed on the basis of regulatory good practices and tips. Compliance with these suggestions, could potentially improve the pace of industry assay development and further certification. It is important to remember, that seamless fulfilment of many of legal obligations require input from scientific stages of development, therefore the application of regulatory guides by a researcher is substantial. Regulatory tasks, pointed out in the specific phase, provide only a cursory overview of the requirements to fulfil. Therefore, in order to obtain a comprehensive overview, content should be considered in conjunction with chapter 4 "IVDR overview" and IVDR itself. General scheme of regulatory affairs in the commercialization process approach can be found below:

Figure 7: Regulatory pathway of the commercialization process approach for IVD biomarkers

PHASE 1 Biomarker discovery	**PHASE 2** Biomarker verification and preliminary scientific validity studies		**PHASE 3** Development of a specific biomarker assay (prototype)	**PHASE 4** Clinical performance of a prototype in laboratory settings		**PHASE 5** Pre industrial maturation phase	**PHASE 6** Industrial assay development	**PHASE 7** Commercial launch and clinical implementation
Start to generate good quality data from beginning of the process in order to make data findable, accessible, interoperable and reusable.	When research results indicate that an analyte meets intended purpose(s) of IVD medical device put focus on documenting of scientific validity as well as familiarizing with requirements for analytical (CLSI standards) and clinical performance evaluation of IVDs, specifically the scientific validity of an analyte and clinical benefit rely on documentation such as publications and reports.	**ACCEPTED INITIAL DESIGN**	Preliminary classification of the progressive product under IVDR rules (relevant risk class), determination of relevant GSPRs and conducting of associated studies. Manufacturer registration is made. Capacity of notified body is checked.	Conduct analytical & clinical studies of IVD medical device. Applying for UDI codes. Part/component drawings, assembly drawings as well as packaging drawings are generated. Labels are designed.	**PROOF OF CONCEPT**	Selection of business model is made. Roadmap for IVDR implementation/IVDR trainings is prepared. Review of supply chain regulations and role of business partners (economic operators) are established. QMS systems established. Registration of device is made.	Final classification of the product and validation of GSPRs studies are conducted. Validation of analytical and clinical performance is performed. Technical documentation is ready for regulatory submission. The PRRC is employed.	The conformity assessment route for the IVD medical device is chosen. Certificates of conformity assessment are obtained. The CE mark is affixed. Certificate of free sale is prepared. UE declaration of conformity is prepared. Notification to the competent authority is made. **PRODUCT IS PLACED ON THE MARKET.** Continuous process of fulfilling obligations regarding the post market surveillance system and vigilance requirements.

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3.1 Commercialization process: Biomarker Discovery phase

The first stage of commercialization process, in respect to the model adopted by the BIC consortium, is the **discovery phase**. The main stakeholder involved at this stage of commercialization is the **researcher**.

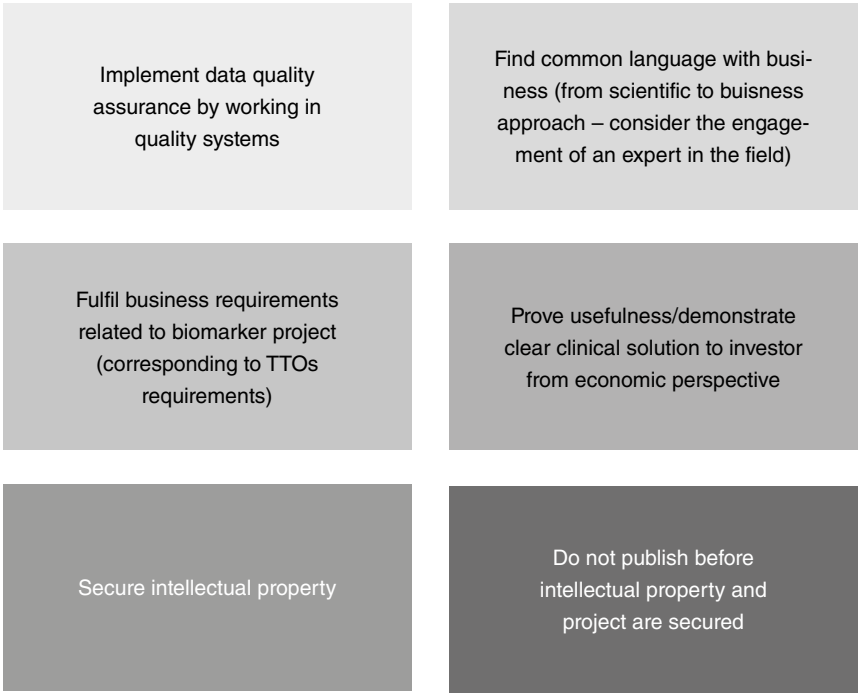
BACKGROUND:

Conducted BIC interviews indicate that researchers usually look at the development of biomarkers from strictly scientific perspective and they are not aware of regulatory affairs. Despite the fact that researchers are not legally responsible for IVDR requirements, researchers obtaining R&D results which have IVD commercial potential, should be aware of the scientific, as well as, regulatory and economic aspects accompanying biomarker projects. This knowledge, as well as other stakeholders expectations, are required if they intend to exploit the commercial potential. If the project is more formalised (properly documented and adjusted to business, as well as to legal requirements), it becomes more attractive for potential business partners and its market value rises. However, first of all (from a regulatory perspective), **researchers should document stringently each biomarker discovery as if it becomes a final IVD medical device.**

The **researcher**, from the beginning of the biomarker project, **is responsible for collecting high-quality and relevant data (as input for further technical documentation), which will result in the conformity assessment** further in the process.

In order to assure effectiveness of the commercialization process, researchers should follow certain principles (fig. 8).

Figure 8: Suggested principles for researchers



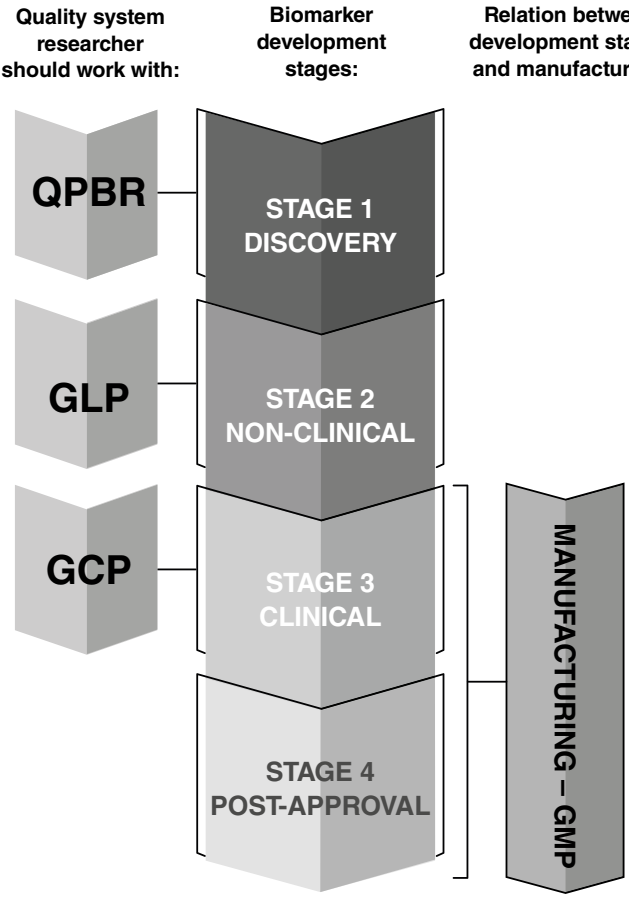
Sources: BIC interviews

QUALITY DATA ASSURANCE:

The researcher should work in quality standards relevant for non-clinical studies (at this stage), and corresponding to those standards, required by a potential business partner and those which faciliate the fulfilment of legal obligations come from the Quality Management System dedicated to IVD medical devices, e.g.: **QPBR** and later in compliance with **GLP** or other principles assuring quality and are accepted by industrial partners (e.g. **FAIR**. The quality assurance approach makes research results more reproducible and transferable to industry. Detailed GLP information can be found in in the GLP handbook released by WHO:

https://www.who.int/tdr/publications/documents/glp-handbook.pdf .

Figure 9: Relation between non-clinical study stages and quality systems recommended for implementation by researchers/manufacturers



Sources: Adopted from WHO GLP Handbook

KEY:

Stages 1 & 2 of biomarker development concern (academic) **researcher**.

REGULATORY TASKS REGARDING DISCOVERY PHASE

1 REGULATORY TASKS TO FULFIL WITHIN 1ST COMMERCIALIZATION STAGE

- **Familiarize with general information regarding the early stages of development from the regulatory perspective**
  Early stages of the IVD assay commercialization process, that do not involve the participation of a company, do not have mandatory regulatory tasks regarding placing a product on the market (as required by IVDR). Please note that, manufacturers bear the burden for ensuring compliance with all regulations during the commercialization process, however if researchers fail to maintain the IVD development standards, the manufacturers could be forced to duplicate/repeat efforts when submitting for approval.

  While not regulated or legally mandated, this is a good point to begin to consider possible regulatory pathways to get a product based on your biomarker discovery on the market. Alongside these considerations, to accelerate eventual regulatory approval, you should seek to comply as soon as possible with standard best practice guidelines (see more in this section, task "Good Practices") regarding conduct of your research.

- **Consideration for ethical approvals for using biological material**
  At present there is no European framework on the use/bio-banking of biological materials and your project may be subject to national regulations that may vary across member states. To assure compliance:

  - check if you have the appropriate and current approvals for the use of data, material, samples etc. to start your project;
  - consider if you are planning on transnational/cross-border exchange of samples. If yes, additional requirements could arise;
  - consider what is the standard and if there is a difference difference between applying for ethical approval for a whole research project or single medical experiment. These requirements can vary significantly across nations/regions.

- **Consideration for patent filling**
  For any invention of newly discovered biomarkers, align patent filing by crafting claims that meet future intended uses/ purposes/ indications for use of a potential IVD medical device. Patent claims ideally cover technology and use claims. These ideally should mimic future intended use claims of IVDs to make patent infringement very obvious.

GOOD PRACTICES

- **Pay attention to competences and responsibilities of your team members**
  Regulatory approval requires specialist knowledge given the breadth and depth of regulatory practices currently in place in the industry (e.g. IVD development standards). Consider how and who should handle these various procedures. The key responsibility of the researcher will continue to be conducting well documented experiments.

- **Work according to a quality system for non-clinical studies and IVD methods**
  Familiarize yourself and your team with popular standards and norms: e.g. QPBR, GLP, FAIR (for scientific data management and stewardship), ISO standards. Where possible, research should be carried out in conformity with current standards and IVD methods. It is recommended to implement a quality system and/or a data management & stewardship system. Well-structured raw data and availability, facilitate further comparisons, validation and reduce differences in re-tests. Consider if there is any specific rule that has to be complied with. Remember that regulatory approval agencies certify only those IVD medical devices which are backed by reliable data generated by the researcher/would-be commercial entity in accordance with IVD standards. Failure to comply with these standards may result in requests for new data.

U.S. standards: CMS/CLIA, CLSI
In the U.S., quality control of the laboratory process, requirements for technicians and proficiency are under CLIA regulation. Compliance with CLIA standards are not obligatory in the EU, but provide comprehensive standards in the field. On the other hand, you can also benefit from using CLSI, which participates in the development of international ISO standards.

More information can be found here:
https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/Clia/

and here:
https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia

and here:
https://clsi.org/

Another standards: EN 13612:2002
"Performance evaluation of in vitro diagnostic medical devices"

- **Consider what is the standard and if there is a difference between applying for the ethical approval of a whole research project or for individual experiments. In some countries, these situations are considered separately.**

The ethical issue table- checklist to consider, can be found here:

https://ec.europa.eu/research/participants/portal/doc/call/h2020/msca-rise-2014/1597696-ethics_issues_table__checklist_en.pdf

3.2 Commercialization process: Biomarker verification and preliminary scientific validity studies

The second stage of the commercialization process, in respect to the model adopted by the BIC consortium, is **biomarker verification and preliminary scientific validity studies**. The stakeholders predominantly involved at this stage of commercialization are: **researchers** and, additionally, **Technology Transfer Offices (TTOs)**.

BACKGROUND:

This stage of development encompasses verification of the identified biomarker and its specificity. From the commercial point of view, it is an appropriate time to analyse the competitive landscape and its novelty, what usually is a field of cooperation between the researcher and experts (in case of academic researchers, usually TTO). TTOs assist in commercial assessment of the biomarker project and help in securing intellectual property or to find additional sources of funding.

REGULATORY TASKS REGARDING BIOMARKER VERIFICATION AND PRELIMINARY SCIENTIFIC VALIDITY STUDIES PHASE

2 REGULATORY TASKS TO FULFIL WITHIN THE 2ND COMMERCIALIZATION STAGE

- **Revisit regulatory strategy**
  While there are no mandatory tasks regarding regulatory aspects of commercialization, this is a good point to re-visit or review your regulatory strategy and approach:

  - what standards are relevant for your geographies of interest?
  - who will oversee the regulatory process in your team/organization?
  - what standards of best practice have you/should you implement?

  Application of industry best practices from an early stage should smooth later stages of commercialization and interactions with regulatory agencies and partners.

GOOD PRACTICES

- **Review and implement good practices from Phase 1**
- **Observe commercial and clinical parameteres of your biomarker.** Positive parameters should reflect in your regulatory engagement.

3.3 Commercialization process: Development of a specific biomarker assay (prototype)

The third stage of the commercialization process, in respect to the model adopted by the BIC consortium, is **development of a specific biomarker assay (prototype).** The BCVC stakeholders predominantly involved at this stage of commercialization are **researchers & Technology Transfer Offices** (eventually, a technical partner from industry could be involved).

BACKGROUND:

At this stage of development, a first working prototype of the product is underway. Meanwhile, the technology will parallelly be assessed for patentability and the scope of patent protection will be decided, usually with the help of TTO* (more information on IPR can be found in chapter 5 of the BIC Best Practice Handbook, available at bic.biomarker.nu). From a regulatory perspective, it is an appropriate time to determine if the assay meets the definition of an IVD medical device (assay becomes an IVD medical device once the intended use/ intended purpose is crafted meeting art. 2(2) & 2(12) of IVDR). Moreover, it is important to collect analytical performance data under the IVDR requirements in order to avoid further adjustments.

REGULATORY TASKS REGARDING DEVELOPMENT OF A SPECIFIC BIOMARKER ASSAY (PROTOTYPE) PHASE

3 REGULATORY TASKS TO FULFIL WITHIN THE 3RD COMMERCIALI-ZATION STAGE

- **Determine if the assay is under jurisdiction of EU IVDR**
  Start by defining the intended purpose of further product. It determines the qualification of your product as IVD or not. Apply article 1 "Subject matter and scope", article 2 (2) "Definitions", article 5 (5) "Placing on the market and putting into service", article 47 "Classification of devices" and if uncertainty exists, article 3 "Regulatory status of products" of IVDR. Answer if the assay intended for examination of blood or other tissue specimens derived from the human body? Does it provide information on any of the following:
  - a physiological or pathological process or state
  - congenital physical or mental impairment
  - predisposition to a medical condition or disease
  - determine the safety and compatibility with potential recipients
  - predict treatment response
  - define or monitoring therapeutic measures.

- **Collect data related to the analytical performance of the assay in respect to IVDR requirements**
  Analytical performance data have to meet specific criteria as stipulated by the IVDR. Apply annex I chapter II no. 9.1 (a) & 9.3 "Performance characteristics" and annex II no. 6.1 "Information on analytical performance of the device" of IVDR. When planning analytical (and clinical) performance studies, remember to take into account IVDR requirements in that field. Well-structured raw data concerning specific characteristics is necessary to provide and constitute essential input for the technical documentation. The analytical performance, such as analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions.

Additional material in order to familiarise with technical documentation requirements at this stage:
Chapter 10.1 of GHTF/SG1/SG1/N063:2011 "Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices"

- **Collect data for justification of scientific validity of a progressing assay**
  Apply annex XIII "Performance evaluation, performance studies and post-market performance follow-up", part A (no. 1.2.1) "Performance evaluation, performance studies" of IVDR.

Follow state of the art e.g. GHTF guideline on scientific validity determination GHTF/SG5/N7:2012.

- **No mandatory regulatory requirements to fulfill within IVDR, until SME involvement in the process.**
  If you wish to track regulatory activities reserved for manufacturers please look at 'Good practices' module.

GOOD PRACTICES

- **Prepare an overview of the regulatory process and implement quality management system**
  Apply articles 10-16 of IVDR and sub-chapters 3.1 – 3.7 of Regulatory Guide. Manufacturer is obliged to implement formal Quality Management System (QMS) for medical devices by using ISO 13485:2016. Note that risk management system and usability engineering approach are foundations of appropriate QMS.

- **Appoint person responsible for regulatory compliance within your institution (not relevant for micro and small enterprises).**
  Apply article 15 "Person responsible for regulatory compliance" of IVDR. If it is confirmed that the product is within the scope of IVDR and the biomarker (research result) is already considered as a product, it is a good

time to recruit a person responsible for regulatory compliance, who possesses the requisite expertise in the field of IVD medical devices.

Guidance on article 15 regarding a person responsible for regulatory compliance can be found here:
https://ec.europa.eu/docsroom/documents/36166

- **Registration of IVD medical device manufacturer**
  Apply article 26 "Registration of devices" & article 28 "Registration of manufacturers, authorised representatives and importers" of the IVDR; sub-chapter 4.2.1 of Regulatory Guide. Proceed through the registration procedure within the EUDAMED database.

- **Familiarize with regulations**
  Familiarize yourself and your team with the IVDR definitions, obligations and requirements by using source document or other guidelines. ISO 18113 could be helpful here, as well.

- **Develop the roadmap for IVDR implementation, including resource requirements, steering group and distribution of responsibility for the implementation of IVDR.**

- **Familiarize with alternative pathways of commercialization**
  For example most of IVDR requirements do not apply to devices manufactured and used only within health instiutions. More on the alternative pathways of commercialization you can find in BIC Best Practice handbook available at biomarker.nu/best-practices.

- **Identify and start demonstrating compliance with GSPRs applicable to progressing product**
  Identification of relevant GSPRs enables to define the severity of work required to demonstrate progressing product will be safe and effective. GSPRs are generic principles and need to be translated into specific requirements of particular product. Start to demonstrating compliance by applying harmonised or other international IVD standards. Full list can be found in Annex I "General safety and performance requirements" of IVDR.

3.4 Commercialization process: Prototype performance in laboratory settings

The fourth stage of the commercialization process, in respect to the model adopted by the BIC consortium, is **prototype performance in laboratory settings**. The BCVC stakeholder involved at this stage of commercialization is the **researcher**.

BACKGROUND:

At this stage clinical performance studies are conducted and most of the product characteristics are determined. On the basis of assay characteristics and risk related to its use, the researcher should be engaged in preliminary classification of the product into one of the IVD risk classes: A, B, C or D and establish relevant/irrelevant GSPRs. The final classification will be carried out by invested enterprise, after their own verification studies are conducted.

REGULATORY TASKS REGARDING PROTOTYPE PERFORMANCE IN LABORATORY SETTINGS PHASE

4 REGULATORY TASKS TO FULFIL WITHIN THE 4TH COMMERCIALIZATION STAGE

- **Check if the obtained ethical approvals still cover the new studies**
  Revise the appropriateness and scope of previously obtained ethical approvals against clinical parameters research. If necessary, obtain new ethical approval and patient consent for your clinical studies release by ethical committee.

- **Collect data related to clinical performance of the prototype**
  During your studies take into account requirements of annex I chapter II (9) of the IVDR. During clinical (and analytical) performance studies, consult IVDR requirements in that field. Well-structured raw data concerning specific characteristics is necessary to provide and constitute essential input for technical documentation to provided by entrepreneur.

- **No mandatory regulatory requirements to fulfill within IVDR, until SME involvement in the process**
  If you wish to track regulatory activities reserved for manufacturers please look at ‚Good practices' module.

GOOD PRACTICES

- **Get start and maintain performance evaluation**
  Performance evaluation is conducted to ensure device is safe and performing for its intended use. It is a continuous process consists of 3 elements and by which those elements needs to be demonstrated: scientific validity, analytical performance and clinical performance. For performance evaluation apply EN 13612:2002 "Performance evaluation of in vitro diagnostic medical devices". Clinical performance studies shall be performed unless it is justified why a demonstration based on other sources of clinical data is sufficient.

  If relevant, fulfil requirements for clinical studies of IVD medical devices and submit he application according to figure 21 of Regulatory Guide and article 66 "Application for performance studies" of IVDR. Start testing by applying ISO 20916:2019 "In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practices". Where relevant, take into account results from earlier phases of development.

- **Applying for UDI codes of the IVD medical device**
  Apply article 24 "Unique Device Identification system" & article 26 "Registration of devices" of IVDR and start process of IVD medical device registration by applying for UDI codes. UDI codes are elements of the new IVDR approach related to devices identification.

- **Complete the device technical description**
  Design device's label and instructions of use. Apply annex I chapter 3 "Requirements regarding information supplied with the device" of the IVDR. Complete the device description which includes device description part/component drawings, assembly drawings and packaging drawings, as well as key components and its operating principles.

- **Perform classification of the assay into risk classes according to IVDR guidelines**
  Apply article 47 "Classification of devices" and annex VIII "Classification Rules" of IVDR and follow figure 29 of the Regulatory Guide. Note:
  - IVD biomarker applicable assays typically fall into classes C or D of the four available classes (A, B, C and D);
  - classification into relevant risk class determines the regulatory pathway;
  - preliminary classification could be expected by a business partner.

  Consider involvement of regulatory specialist.

- **Determine a regulatory pathway for the product**
  Apply article 48 "Conformity assessment procedures" of IVDR and follow figure 30 of the Regulatory Guide. Note that the regulatory pathway depends on risk class and intended use of the product. Continue to monitor progress of the IVDR implementation plan.

3.5 Commercialization process: Pre-industrial maturation phase

The fifth stage of the commercialization process, in respect to the model adopted by the BIC consortium, is **pre-industrial maturation phase**. The BCVC stakeholders predominantly involved at this stage of commercialization are **researcher**, TTO and **enterprises**, as participants of technology transfer.

BACKGROUND:

The pre-industrial maturity phase is quite short on a technical level, but may take time during the commercial portion (preparation of business plan, due diligence, negotiation, etc.). At this stage of development technology transfer takes place. The researcher has to consider commercialization pathways. Legal aspects of starting a company, licensing, etc., are considerations for the commercial aspects of BIC Guide (available at https://bicguide.biomarker.nu/). If you plan on establishing a spin-out, you should begin by following the regulatory obligations.

REGULATORY TASKS REGARDING THE PRE-INDUSTRIAL MATURATION PHASE

5 REGULATORY TASKS TO FULFIL WITHIN THE 5TH COMMERCIALIZATION STAGE

- **The stage concerns technology transfer – no mandatory regulatory requirements to fulfill within IVDR, until SME involvement in the process.**
  If you wish to track regulatory activities reserved for manufacturers please look at "Good practices" module.

GOOD PRACTICES

- **Initiate the notified body selection process**
  It may take up ¾ of a year from first contact to closure of an agreement. Use the NANDO database. Number of IVDR designated notified bodies is very limited, and vary in the term of competences and scope of assessment. It may take up ¾ of a year from first contact to closure of an agreement. Use the NANDO database. Number of IVDR designated notified bodies is very limited, and vary in the term of competences and scope of assessment. Check the availability/capacity of the notified body before submitting the application.

- **Review the supply chain regulations and clarify the roles and responsibilities of business partners (authorized representatives, distributors, importers).**

In order to search for potential authorised representatives, the EAAR database can be used:
http://www.eaarmed.org/

- **Registration of authorised representatives and importers**
  Remember of required registration of authorised representatives and importers according to article 28 "Registration of manufacturers, authorised

representatives and importers" of IVDR. According to article 27 (2) "Electronic system for registration of economic operators" of IVDR, Member States may maintain or introduce national provisions on registrations of distributors of devices which have been made available on their territory.

- **Conduct regulatory training for any new team members.**

Helpful materials in getting acquainted with the regulatory affairs can be found here:
https://ec.europa.eu/growth/sectors/medical-devices_en

A Factsheet for Manufacturers of in vitro Diagnostic Medical Devices providing a brief overveiw on the regulatory requirementsunder IVDR can be found here:
https://ec.europa.eu/docsroom/documents/33662

In the case of regulatory overview also CAMD IVDR roadmap could be helpful, it can be found here:
https://www.camd-europe.eu/wp-content/uploads/2018/05/NEWS_171107_MDR-IVDR_RoadMap_v1.3-1.pdf

NOTE

- Seriously consider markets and their sizes for the product, e.g. if there is a chance to reach the U.S. market, follow FDA requirements from the beginning of your project. More information about FDA requirements can be found here:

https://www.fda.gov/medical-devices/ivdregulatory-assistance/overview-ivd-regulation

3.6 Commercialization process: Industrial assay development

The sixth stage of the commercialization process, in respect to the model adopted by the BIC consortium, is **industrial assay development**. The BCVC stakeholder involved at this stage of commercialization is **either the spin-out or the established company assigning the research results.**

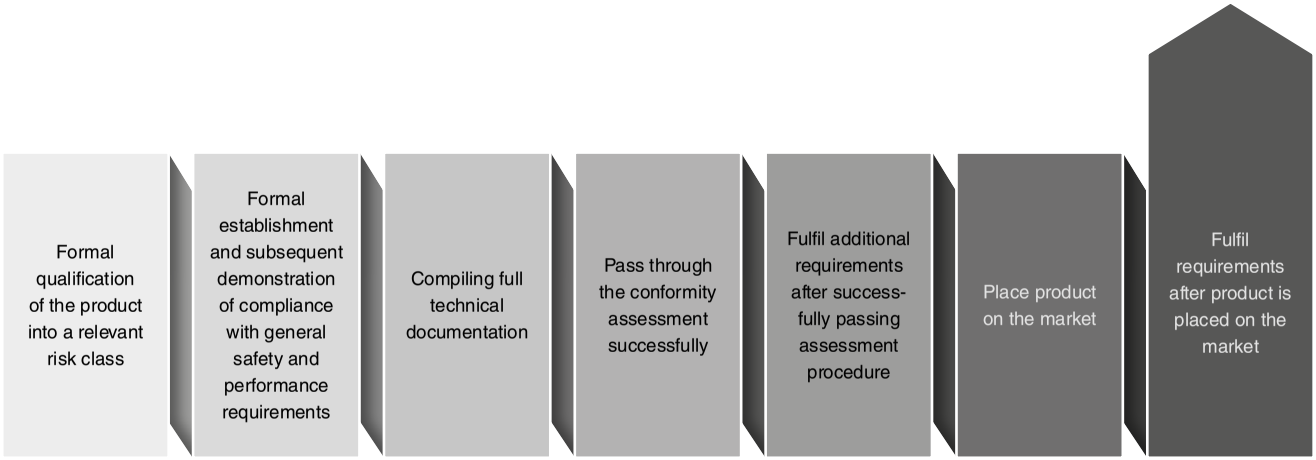
BACKGROUND:

At this stage of development mandatory regulatory obligations appear and automatically the involvement of an enterprise emerges. **It has to be stated very clearly, that IVDR is particularly dedicated to enterprise**, which is responsible for legally fulfilling the regulatory requirements and placing the final product on the market.

An IVD medical device has to fulfil a number of requirements, however, compliance demonstration occurs when the product successfully passes conformity assessment procedures. Conformity assessment is based on evaluation of the QMS and completed device **documentation** gathered by the manufacturer. It should therefore be stated, **that the proper collection of full technical documentation** is the main task a manufacturer has to face. In practice, the enterprise is responsible for the formal approval of relevance of objective general safety & performance requirements, formal determination of the IVD medical device into a risk class (based on researcher's input) and for developing the full technical documentation (in respect to general safety & performance requirements and QMS). The documentation is subsequently assessed by a notified body within the conformity assessment procedure for most IVD medical devices (all other than non-sterile class A IVDs). Consulting firms may help with audit preparation and/or in 'conformity assessment readiness' well before notified body review of the submission. These types of services are quite expensive, and come on top of further costs associated with conformity assessment. Such cost are e.g. review and audit fees of notified bodies where currently only 4 NBs have been designated for IVDR (september 2020).

To provide an overview of the regulatory affairs activities of the enterprise involved in the commercialization process, a general overview is introduced on the next page:

Figure 10: Milestones in IVD medical device development for an enterprise from a regulatory perspective



Sources: IVDR

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REGULATORY TASKS REGARDING INDUSTRIAL ASSAY DEVELOPMENT PHASE

6 REGULATORY TASKS TO FULFIL WITHIN THE 6TH COMMERCIALIZATION STAGE

- **Verify the usefulness of data & results from research phases**
  Check the completeness and quality of the data. Verify that the data meets the critical criteria and determined research methods. Verify which data & results you can use for purpose of the development of technical documentation.

- **Conduct product verification & validation studies**
  Verification studies encompass reviewing, inspecting and testing the components, processes and final device in order to confirm the device agress with requirements. Validation proces follow verification and ensure the device functions as intended in real-life conditions.

- **Conduct production testing**
  Aim of production testing is to determine if the product is correctly manufactured and ensure that all of the product designs are translated into manufacturing specifications. Generated documentation constitute the integral part of Technical Documentation and could be reviewed during conformity assessment.

GOOD PRACTICES

- **Check what the standard language is for the documentation in the Member State in which the notified body is established, as well as in Member States where the device is expected to be sold**

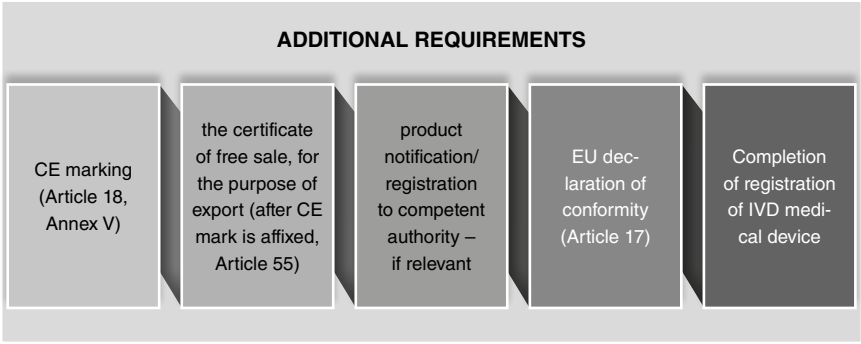
3.7 Commercialization process: Commercial launch and clinical implementation

The seventh stage of the commercialization process, in respect to the model adopted by the BIC consortium, is the **commercial launch and clinical implementation**. The stakeholder predominantly involved at this stage of commercialization is **the enterprise.**

BACKGROUND:

The manufacturer's efforts on achieving compliance is not enough. It just triggers continuous work during life cycle of the medical device. After successful certification, the enterprise is also responsible for addressing additional requirements before the product appears on the market (e.g. CE marking) and maintain post-market surveillance activities. In order to place an IVD biomarker product onto the market the manufacturer must address the additional following requirements:

Figure 11: Additional requirements to fulfil after a product has successfully passed the conformity assessment procedure



NOTE

In the case if EUDAMED will not be fully operational by the IVDR date of application, further national registrations may be required.

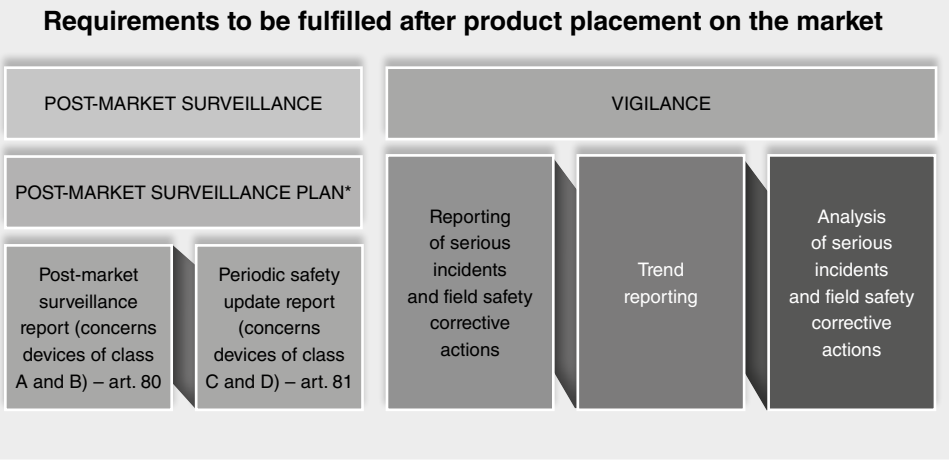
Sources: IVDR

Maintenance of compliance throughout life cycle

Post-market surveillance (PMS) is a broad concept and includes many different concepts to ensure patient safety after a medical device has been placed on the market. It includes vigilance activities, feedback handling and post-market performance follow-up (PMPF) for IVDs. It also takes the form of various different types of reports.

Post-market surveillance system is an integral part of the manufacturer's QMS and facilitates the collection and analysis of data on quality, performance and safety of the device. Post-market surveillance for a specific device shall be based on a post-market surveillance plan. Manufacturer is obliged to report on the results and conclusions based on post-market surveillance data in the form of post-market surveillance report (manufacturers of class A and B devices) or Periodic Safety Update Report (manufacturers of class C and D devices). The purpose is also to provide a rationale and description of any corrective and preventive actions (CAPA) taken.

Figure 12: Requirements (direct) to be fulfilled by the enterprise after a product is placed on the market



Sources: IVDR

Vigilance is extremely important to maintain product safety in problematic situations. The procedure can prevent the occurrence of injuries and other adverse effects on patients and end users in general. After the product has been placed on the market, the manufacturer's most important responsibility is considered to be the ability to perform vigilance: To take appropriate measures and submit timely incident reports when necessary. The manufacturer and, if applicable, their authorised representative must take actions effectively and in a timely manner within a strict framework. A good rule of thumb is to make one too many incident reports than one too few. Patient safety must not be compromised!

Articles 82-87 of IVDR set requirements for vigilance process and reporting, where article 82 regards to adverse events, article 83 to reporting on trends, and article 84 to field safety corrective actions – FSCA.

MEDDEV 2.12-1 rev 6 Guidelines on a Medical Devices Vigilance System provides also useful information to manufacturers even though the reporting system will be replaced by EUDAMED registry.

NOTE

- Post-market surveillance plan is a part of technical documentation and have to be submitted to a notified body in order to pass conformity assessment.
- PMS, vigilance and market surveillance obligations have to be fulfilled for legacy devices certified under IVDD as well (article 110(3)) as of 26 May 2022.
- Majority of IVDs that are already on the market as class I devices under IVDD will be re-classified under IVDR as burdened with higher risk. Hence technical documentation including PMS Plan will have to be submitted to a notified body before 26 May 2022.

REGULATORY TASKS REGARDING COMMERCIAL LAUNCH AND CLINICAL IMPLEMENTATION PHASE

7 REGULATORY TASKS TO FULFIL WITHIN THE 7TH COMMERCIALIZATION STAGE

- **Pass through conformity assessment procedure successfully**
  Conformity assessment procedures differ in complexity and scope and its extent is driven by risk class and intended purpose of the device. Follow the prior determined regulatory pathway. Choose the notified body from the NANDO system and submit application for conformity assessment. Cooperate with the notified body in order to pass the procedure. After successful certification draw up EU declaration of conformity according to article 17 "EU declaration of conformity".

- **Address the additional requirements before placing device on the market**
  After successful conformity assessment, the manufacturer is responsible for addressing additional requirements before device appears on the market, as following:
  - **CE mark**
    Go forward with CE marking in line with Article 18 "CE marking of conformity" and Annex V "CE marking of conformity" of IVDR.
  - **Certificate of free sale**
    Details on certificate of free sale can be found in Article 55 "Certificate of free sale" of IVDR.
  - **EUDAMED registration**
    Complete the registration according to Article 26 "Registration of devices" and Article 28 "Registration of manufacturers, authorised representatives and importers" of IVDR.

- **Maintain of compliance throughout life cycle**
  Post-market surveillance (PMS) is a broad concept and includes many different concepts to ensure patient safety. Through PMS manufacturer is obliged to report on the results and conslusions based on gathered data in the form of post-market surveillance report (manufacturers of class A and B devices) or Periodic Safety Update Report (manufacturers of class C and D devices). The purpose i salso to provide a rationale and

description of any corrective and preventive actions (CAPA) taken. More information can be found in article 78 "Post-market surveillance system of the manufacturer" of IVDR.

Vigilance is extremely important to maintain device safety in problematic situations. Vigilance obligations encompass reporting on adverse events, trends as well as analysis of serious incidents and field safety corrective actions. More information can be found in articles 82-87 of IVDR.

- **Cooperate with national entities to ensure safety (market surveillance requirements)**
  It is a continuous process supervised by competent authorities. Prepare for additional requirements/reviews after the product is placed on the market: anticipate for checks on the conformity, characteristics and performance of devices including, where appropriate, a review of documentation and physical or laboratory checks on the basis of adequate samples. Prepare to take all appropriate and duly justified corrective action to bring the device into compliance with the requirements of IVDR. Potentially restrict the making availability of the device on the market, modify the product to specific requirements or to withdraw the device from the market, or to recall it, within a reasonable period that is clearly defined and communicated to the relevant economic operator.

GOOD PRACTICES

- **Check validity of used templates**
- **Remember that the declaration of conformity shall contain all the information required for identification of the European Union legislation to which the declaration relates, therefore, if there are some aspects not covered by IVDR the manufacturer must still draft up single declaration (details as in description)**
- **Monitor the expiration dates of achieved conformity certificates**
- **Continue to actively monitor the regulatory environment for amendments, new requirements etc.**

4

IVDR OVERVIEW

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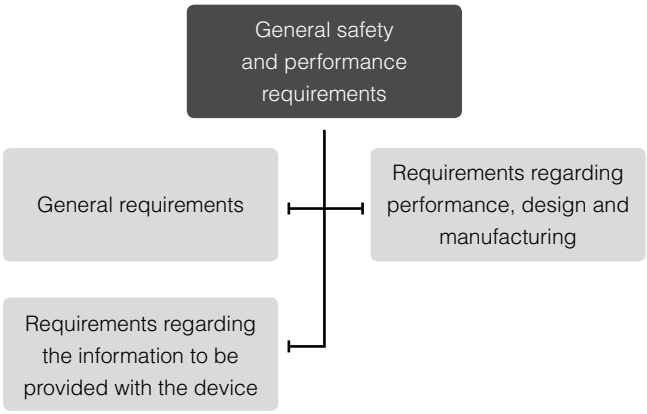
4.1 General safety and performance requirements

The device must meet the applicable General Safety and Performance Requirements (GSPRs), considering its intended purpose. The requirements are generic principles and that need to be translated into specific requirements for your particular product, leaning on possible more specific requirements defined in applicable standards. GSPRs cover functional, as well as performance and interface requirements of the product and its manufacturing environment. It is a good practice to use a checklist prepared for this purpose for assessing applicable requirements for your product and demonstrating that the requirements have been fulfilled (look at IVDR Roadmap). If you deem concrete requirement is not relevant, provide justification. Process of demonstrating compliance with IVDR regulatory requirements begins here. It is also an appropriate time to start fulfilling the general requirements as well, not directly related to the product. Details can be found in annex I of IVDR.

General safety and performance requirements are divided into 3 main groups (fig. 20), and compliance with them can be demonstrated by using appropriate method /methods used:

- **harmonised standards** – recommended solution (if existing)
- common specifications
- other solutions applied in order to confirm the compliance with requirements (other international IVD standards)

Figure 13: General safety and performance requirements structure



Sources: IVDR

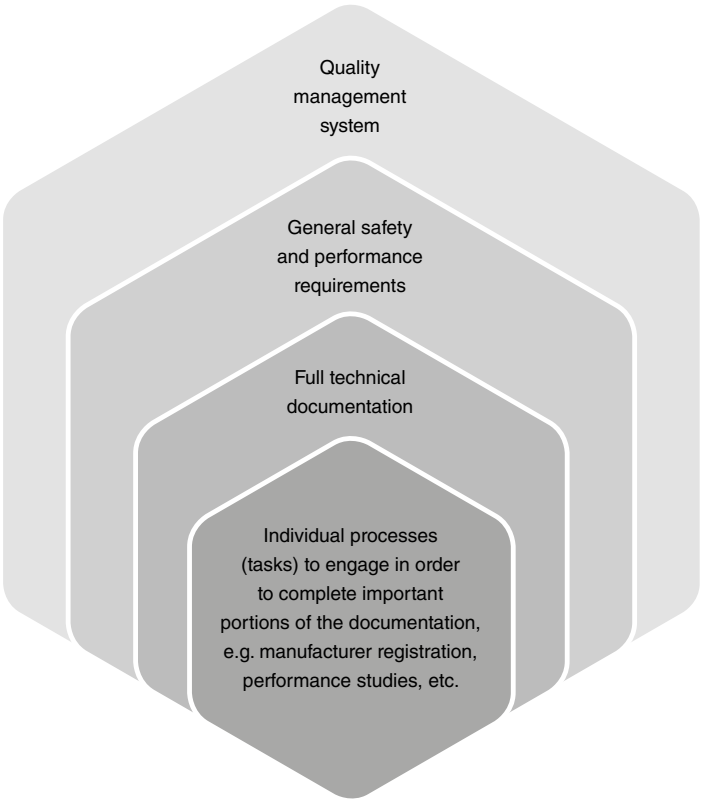
In addition, the entire technical documentation has to be developed in line with the GSPRs. Demonstration of conformity with applicable GSPRs and applied solutions have to be documented as well.

Unfortunately, the variety of medical devices and its characteristics prevent assignment of GSPRs to particular devices in advance. Except of group of products (at appropriate level), the process has to be considered as device-specific.

The component of technical documentation related to general safety & performance requirements includes:

- the general safety and performance requirements that apply to the device with an explanation as to why other requirements do not apply
- the method or methods used to demonstrate conformity with each applicable general safety and performance requirement
- the harmonised standards, CS or other solutions that are applied
- the precise identity of the controlled documents offering evidence of conformity with each harmonised standard, CS or other methods applied to demonstrate conformity with the general safety and performance requirements. The information referred to under this point shall incorporate a cross-reference to the location of such evidence within the full technical documentation and, if applicable, the technical documentation summary.

Figure 14: Relation between QMS, general safety and performance requirements and technical documentation.



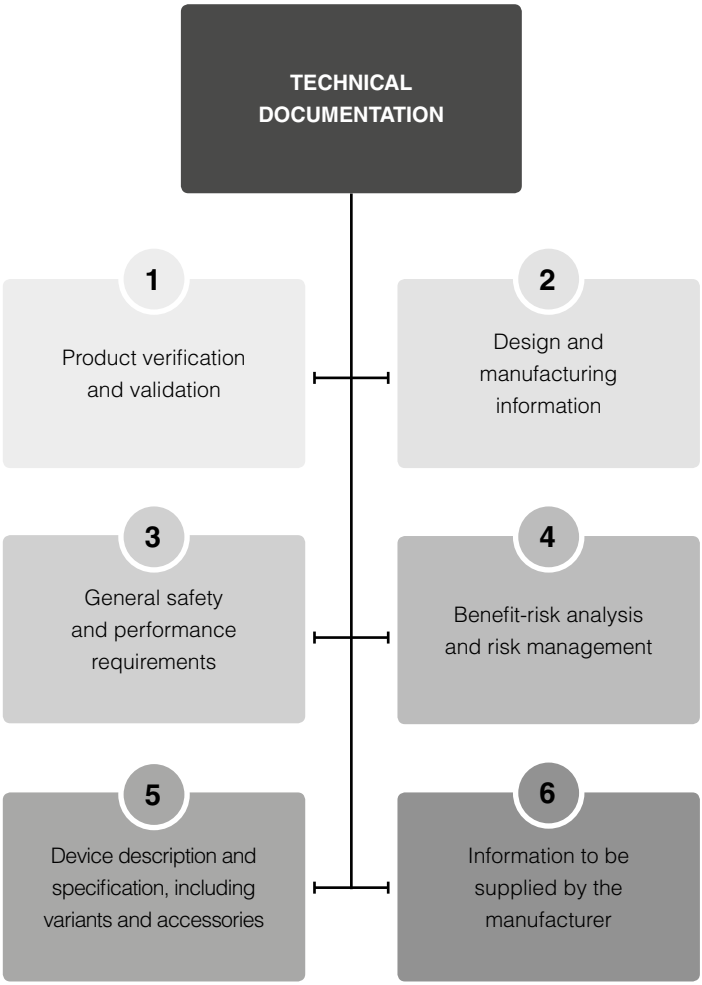
Sources: IVDR

4.2 Technical documentation

The technical documentation of a device (annex II of IVDR) is developed by the manufacturer (if relevant, also in an abbreviated version), and is subject to assessment, which is usually conducted by a notified body.

The technical documentation is closely related to the GSPRs. The structure of the technical documentation required for IVD medical devices is introduced below. Main parts of the technical documentation, and its critical components are indicated below.

Figure 15: Technical documentation of an IVD product – structure



Sources: IVDR

KEY

IVDR stipulates collecting of individual parts of Technical Documentation requires at least:

1. Conducting a performance study and its evaluation (chapter 4.2.2 of RG).
2. Gathering this part of the documentation does not require additional activities (manufacturer description – no further actions is needed).
3. Confirmation of conformity to relevant general safety and performance requirements (chapter 4.1 of RG).
4. Implementation of the risk management system (annex I, chapter I of the IVDR), as a part of the quality system (art.10(8) of the IVDR) for a given company. Proper establishment of risk management requires the conducting of performance studies.
5. **Manufacturer and device registration** in the Eudamed database (chapter 4.2.1 of RG). Registration cannot be completed without the submission of the safety and performance summary as an informational component.
6. Deliver a complete set of the labels to be used on the device and on its packaging and the applicable instructions (in respect to article 7 of the IVDR). The delivered information on the labels requires an UDI carrier.

The dependents of collecting the necessary documentation are introduced below:

Table 1: Dependents of collecting full technical documentation

Technical documentation	**Portion of documentation feasible to complete before manufacturer and device registration**	**Design and manufacturing information**
	Portion of documentation feasible to complete before performance studies report obtained	Information to be supplied by the manufacturer
	Portion of documentation required for conformity assessment	All parts
Technical documentation on post-market surveillance	Portion of documentation required for conformity assessment	Post-market surveillance plan
	Portion of documentation required after IVD medical device placement on the market	Post market surveillance report, Periodic safety update report

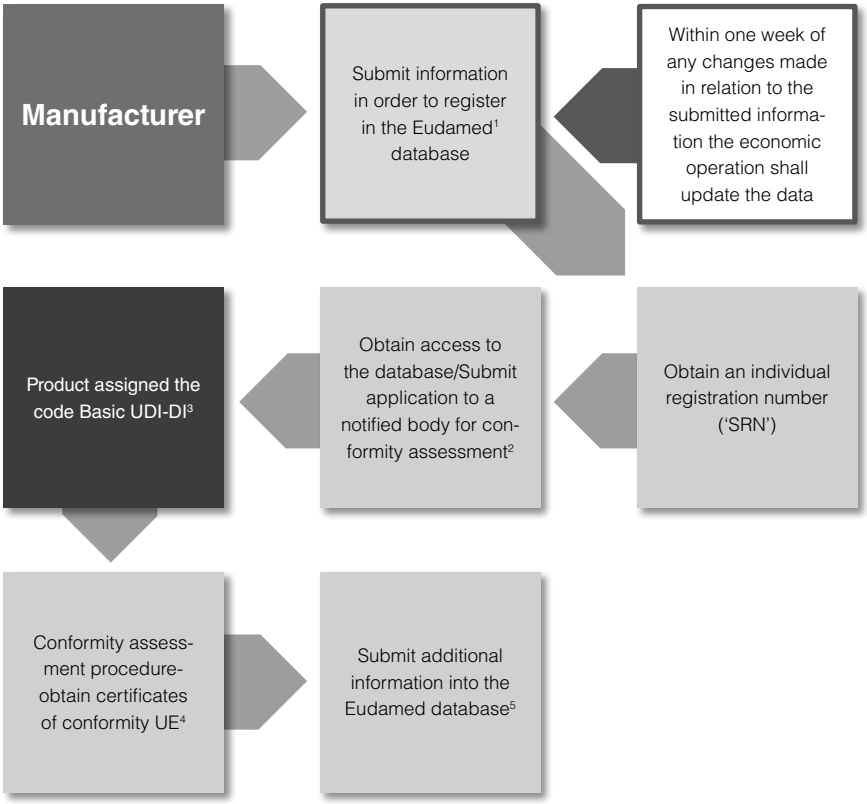
NOTE

- The Post-market surveillance report/Periodic safety update report is due first time one year after 26 May 2022 for IVD medical devices certified under IVDR.
- Post market surveillance report applies to devices of classes A and B, and Periodic safety update report applies to devices of classes C and D
- Voluminosity and complexity of technical documentation and technical documentation on post-market surveillance are specific, and depend on concrete IVD medical device characteristics

4.2.1 MANUFACTURER AND DEVICE REGISTRATION

One of the requirements facilitating the completion of the technical documentation portion called "Device description and specification including variants and accessories" (and indirectly other portions) is **manufacturer and device registration**. The scheme below presents two closely related processes: registration of the manufacturer and registration of the device (look at the key description below).

Figure 16: Manufacturer and device registration



Sources: IVDR

KEY

If the manufacturer is already registered in the European system, the figure applies from the stage "Product assigned the code Basic UDI-DI" in accordance with article 26.

1. Information submitted for registration in the Eudamed database – annex VI, part A, section 1. In cases where the conformity assessment procedure requires the participation of a notified body (class B, C and D of the devices), the information referred to shall be transferred to the system before submitting the application to the notified body – in the order presented in the above diagram.
2. Conformity assessment relevant to the class of device.
3. The manufacturer shall pass this step in accordance with article 26 (Registration of devices). The manufacturer shall, in accordance with the rules of the issuing entity referred to article 24(2), assign a basic UDI-DI to the device as defined in part C of annex VI and shall provide it to the UDI database together with the other core data elements referred to in part B of annex VI related to that device. In the case of devices of: class D (in accordance with art.48(3,4), class C (in accordance with art.48(7) second paragraph, and art. 48(8), class B (art. 48(9) second paragraph) a successfully assigned basic UDI-DI code must be completed before submitting an application for conformity assessment.
4. In the case of the products mentioned in point 3, the notified body places relevant references. After the certificate (certificate of conformity assessment) is obtained and before placing the device on the market, the manufacturer shall provide the UDI-DI code to the Eudamed database (UDI database) together with the other core data elements referred to in annex VI, part B.
5. Before placing the product on the market, the manufacturer shall provide the information to the Eudamed database referred to section 2 of part A of annex VI, with the exception of section 2.2, or – if this information has already been provided, verify and update the information.

Implementation of UDI carriers is the result of the new approach introduced within the IVDR. In comparison to the old Directive, where the UDI system did not apply, traceability and identification of the product will be significantly improved and digitized by the Eudamed database. More information about the UDI system can be found in article 24 and annex VI.

NOTE

The IVDR forecasts the deadline for the implementation of UDI carriers, according to device risk class, respectively for: class D devices- 26 May 2023, class B and C devices- 26 May 2025 and class A devices- 26 May 2027.

FURTHER READING:

Supporting material, as well as guidance on the UDI system can be found here:
https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/guidance_en

European Commission recommendations on a common framework for a UDI system can be found here:
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32013H0172

4.2.2 PERFORMANCE STUDY AND PERFORMANCE EVALUATION

After analysing the level of knowledge of producers, as well as other members of the BCVC, (based on BIC project research/interviews), performance studies and performance evaluation of the progressing product are the most comprehensive activities during the commercialization of a biomarker product. **IVDR is focused on the clinical performance evaluation of a product.** Therefore, this chapter has been extensively developed in order to provide as much information as possible to complete the necessary documentation regarding product verification and validation (fig. 22).

Performance studies are studies conducted in order to determine or confirm analytical or clinical performance. Performance studies serve several purposes (in the context of IVD):

1. to demonstrate the usefulness of an analyte that comply with intended purpose(s) of IVD medical device("determination studies" are usually conducted by the researcher),
2. to confirm a performance claimed by the researcher and proof compliance with IVDR ("confirmation studies" are conducted by producer),

2'. to confirm the performance of D class devices (eventually C class at the request of a Member State) claimed by a producer ("EU reference laboratory studies" are conducted by a notified body via a EU reference laboratory),

or

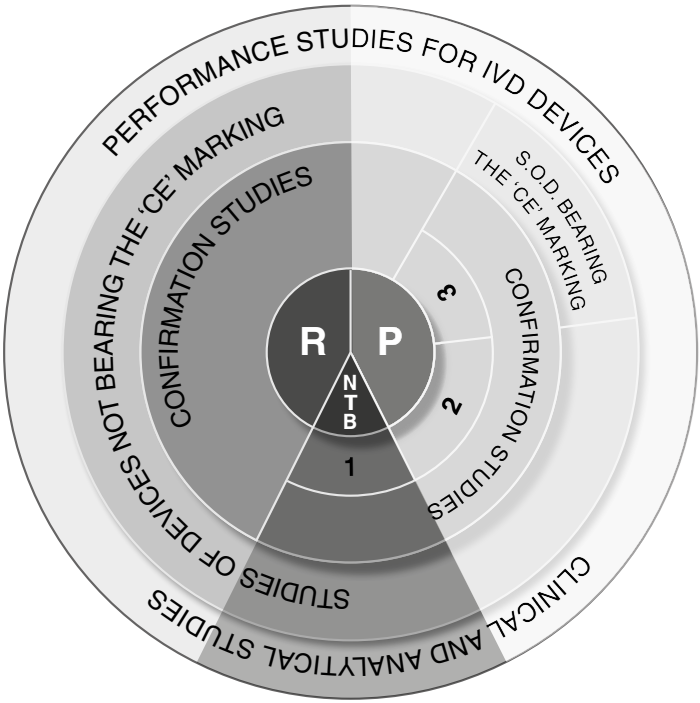
3. to monitor/update performance evaluation throughout the life cycle of a device ("PMPF studies").

The enterprise is responsible for the development of technical documentation concerning product verification & validation, which mostly consists of performance study results (on the basis of (1) and (2)). The documentation is a requirement for submission for conformity assessment. Conformity assessment, which is usually conducted by a notified body, examines performance in the case of high-risk devices by conducting relevant studies (2') and confirming/not confirming the performance claimed by the manufacturer (2). Through the lifecycle of the IVD product, the manufacturer has to fulfil the requirement of updating product performance (3).

Types of performance studies

Depending on the criteria, different types of performance studies can be distinguished:

Figure 17: Types of performance studies and responsibilities of each study



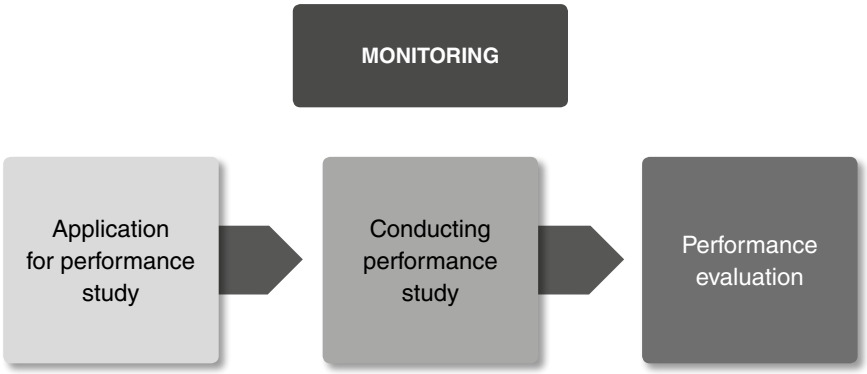
Sources: IVDR, BIC resources

KEY

NTB – Notified Body, **P** – Producer, **R** – Researcher, 1 – **EU** reference laboratory studies, **2** – Verification studies, **3** – PMPF studies, **S.O.D.** – Studies of devices

To facilitate a better understanding of a performance study, the 3-stage process is introduced below:

Figure 18: Performance study process-general scheme



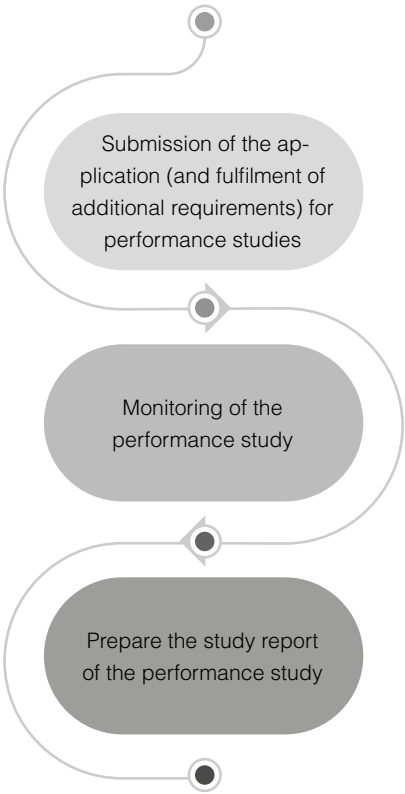
NOTE

- Completed performance evaluation enables completion of technical documentation regarding product verification & validation (and other parts of the documentation, in accordance to figure 21)
- A positive result of clinical trials is a pre-requisite for registration and placing the product on the market

Responsibility for performance studies according to the IVDR

The sponsor (as explained in chapter 1.1) is responsible for the performance study and its evaluation. There is also a possibility of outsourcing the performance studies and delegating them to Contract Research Organizations (CRO) on the basis of a contract.

Figure 19: General role of the sponsor in the performance study process



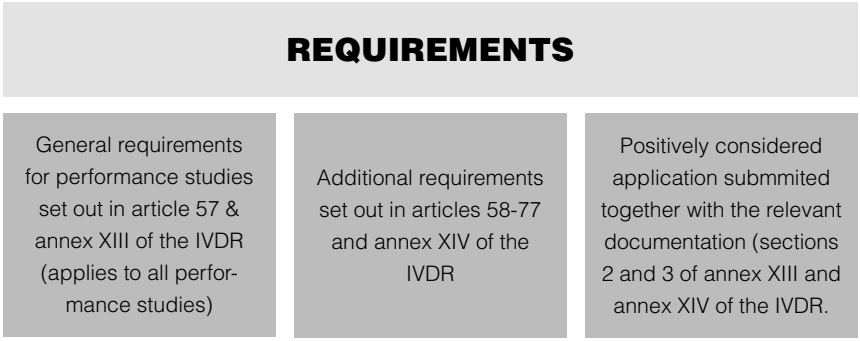
Sources: IVDR

4.2.2.1 APPLICATION FOR PERFORMANCE STUDIES AND ADDITIONAL REQUIREMENTS TO FULFIL BEFORE THE PERFORMANCE STUDY IS INITIATED

The possibility of conducting a performance study necessitates a number of general (article 57, annex XIII of IVDR) and additional (article 58, annex VI of IVDR) requirements, that have to be met before applying for authorisation. First, the sponsor has to fulfil those requirements (relevant for the specific IVD medical device), then has to complete the documentation and finally submit the application.

The application for the authorisation of a performance study has to be submitted (via Eudamed) and successfully deliberated by the Member State, before the performance study may start.

Figure 20: Requirements needed to be fulfilled before a performance study is initiated



Sources: IVDR

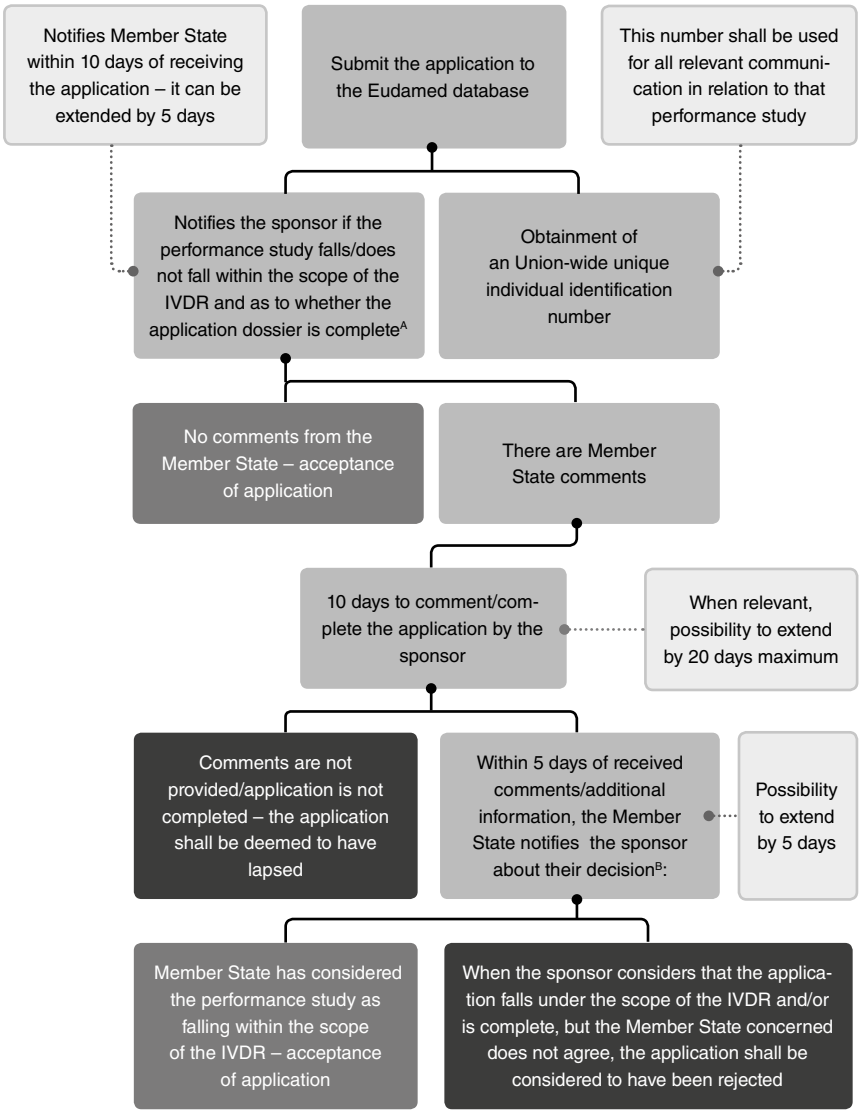
Application

The application for permission to conduct performance studies is submitted to the Member State by the sponsor, using the electronic system for performance testing (article 69 of the IVDR) accompanied by the documentation referred to in sections 2 and 3 of annex XIII and in annex XIV of IVDR.

The sponsor of performance studies that will be conducted in more than one Member State has the right to submit only one application (electronically the application will be forwarded to the other countries), which triggers the coordinated assessment procedure described in article 74 of IVDR.

The procedure for submitting the application for conducting performance studies is present below:

Figure 21: Sponsor application procedure for performance studies



Sources: IVDR

KEY

Dates of notifying the sponsor [A] and [B] are the validation dates of the application. When the sponsor is not notified, the validation date shall be the last day of the periods referred to [A] and [B] (with extensions).

IVDR QUOTE:

During the period when the application is being assessed the Member State may request additional information from the sponsor. The expiry of the deadline pursuant to the point (b) of paragraph 7 shall be suspended from the date of the first request until such time as the additional information has been received.

The sponsor may start the performance study in the following circumstances:

- **a.** *in the case of performance studies carried out pursuant to point (a) of article 58(1) and where the specimen collection does not represent a major clinical risk to the subject of the study, unless otherwise stated by national law, immediately after the validation date of application described in paragraph 5 of this article, provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the performance study;*
- **b.** *in the case of performance studies carried out pursuant to points (b) and (c) of article 58(1) and article 58(2) or performance studies other than those referred to in point (a) of this paragraph, as soon as the Member State concerned has notified the sponsor of its authorisation and provided that a negative opinion which is valid for the entire Member State, under national law, has not been issued by an ethics committee in the Member State concerned in respect of the performance study. The Member State shall notify the sponsor of the authorisation within 45 days of the validation date of the application referred to in paragraph 5. The Member State may extend this period by a further 20 days for the purpose of consulting with experts.*

NOTE

Submission of an application for the authorisation of a performance study of an in vitro diagnostic device is payable and varies from country to country (e.g. in Poland, it costs 5,000 PLN ~ 1180 €). It is a good practice to check the current cost for submitting an application with the competent authority website. Validation and verification of the application are dealt with by the competent authorities of the Member States (list of competent authorities can be found in NANDO database).

4.2.2.2 PERFORMANCE STUDY

Performane studies shall always be performed unless it is justified why a demonstration based on other sources of data is sufficient.

Requirements concerning the scope of the performance studies are determined in the IVDR. An IVD biomarker product shall achieve the performances, as stated by the manufacturer and in particular, where applicable, as described in annex I, chapter II, section 9.1.(a):

IVDR QUOTE:

The analytical performance, *such as, analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions.*

As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies.

For novel markers or other markers without available certified reference materials or reference measurement procedures, it may not be possible to demonstrate trueness. If there are no comparative methods, different approaches may be used if demonstrated to be appropriate, such as comparison to some other well-documented methods or the composite reference standard. In the absence of such approaches, a clinical performance study comparing performance of the novel device to the current clinical standard practice is required.

The clinical performance, *such as diagnostic sensitivity, diagnostic specificity, positive predictive value, negative predictive value, likelihood ratio, expected values in normal and affected populations.*

Demonstration of the clinical performance of a device shall be based on one or a combination of the following sources:

- *Clinical performance studies;*
- *Scientific (peer-reviewed) literature;*
- *Published experience gained by routine diagnostic testing.*

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

The broader definition of analytical performance can be founded in art. 2(40) and clinical performance in art. 2(41).

Documentation

Each performance study is documented through a **performance study plan** (input) and **a** relevant **study report** (output, which is an element that determines the performance evaluation).

Figure 22: Documentation related to performance study

WHAT IS NEEDED TO CONDUCT A PERFORMANCE STUDY?	WHAT IS THE RESULT OF A PERFORMANCE STUDY?
A succesfully assessed application and documentation related to it (a performance study plan is a crucial element of documentation)	Study report

Relation between performance studies and quality standards:

Analytical performance studies, as well as clinical performance studies, and its evaluation, in order to maintain reliability, replicability and quality of the data, shall be conducted in accordance with relevant quality standards e.g. CLSI standards for analytical performance, ISO 20916:2019, EN 13612:2002, IMDRF standards of Good Clinical Practice (GCP) for clinical performance.

4.2.2.3 MONITORING OF PERFORMANCE STUDIES

The performance study is carried out on the basis of its plan, as mentioned in sub-chapter 4.2.2.2.

The sponsor (together with the study staff conducting the studies) have to ensure, that the performance study was conducted in accordance with this plan, moreover, it assesses all the features of the performance study, including:

a. the objective and methodology of the performance study; and
b. the degree of deviation of the intervention from normal clinical practice.

Detailed requirements for conducting performance studies are described in article 68 of the IVDR.

Modification in studies

As part of the performance studies, the sponsor establishes a procedure to be used in emergency situations, which enables the immediate identification and, where necessary, an immediate recall of the devices used in the study.

If the sponsor intends to introduce modifications in the study, that are likely to have a significant impact on participant safety, data reliability, etc. (article 71 of the IVDR) he/she notifies the Member State, via the electronic system, within **one week**[1] informing of the reasons and nature of these changes – updates the documentation referred to in annex XIV of the IVDR, where modifications shall be clearly identifiable. The sponsor may introduce the modifications no sooner than **38 days** whereas the Member State may extend this period by 7 days for consultations with experts) after submission (unless sponsor has obtained a refusal of performance study authorization or a negative opinion on the modification by the ethics committee (article 71 section 3 (a and b) of the IVDR).

Performance studies regarding devices bearing the CE marking

The sponsor is obliged to notify (via Eudamed), along with the included documentation indicated in article 70 of the IVDR, the Member State **30 days** before the performance study is to be conducted, if:

a. the performance study is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking – 'PMPF study' (in accordance with article 70 of the IVDR), and
b. the performance study would involve submitting subjects to additional procedures to those performed under the normal conditions of use of the device and those additional procedures being invasive or burdensome.

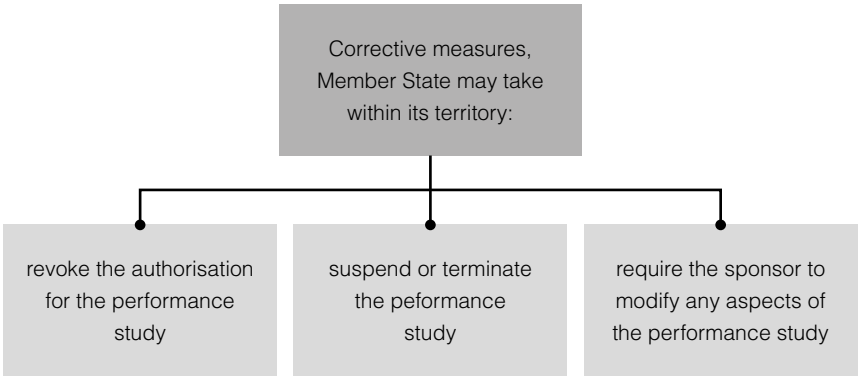
1 The time of one week counts from the date a sponsor decides to introduce changes in the performance studies or receives information on the basis of which he will introduce such changes.

Where a performance study is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking, articles from 58 to 77 of the IVDR shall apply.

Adverse events

The sponsor is obliged to register and report adverse events occurring during the performance testing (if they do appear, it proceeds in accordance with article 76 of the IVDR), however, if the Member State in which the test is or will be conducted has reason to believe that the requirements are not fulfilled (stated in the Regulation), it may adopt appropriate corrective measures within its territory using one of the following measures (more about corrective measures can be found in article 72 of the IVDR).

Figure 23: Corrective measures-structure



Sources: IVDR

4.2.2.4 PERFORMANCE EVALUATION

Performance evaluation is conducted to ensure device is safe and performing for its intended use. It is a continuous process which consists of 3 elements and by which those elements need to be demonstrated: scientific validity, analytical performance & clinical performance. According to article 5 and annex XIII of IVDR, the performance evaluation shall be thorough and objective, considering both favourable and unfavourable data. Its depth and extent shall be proportion-

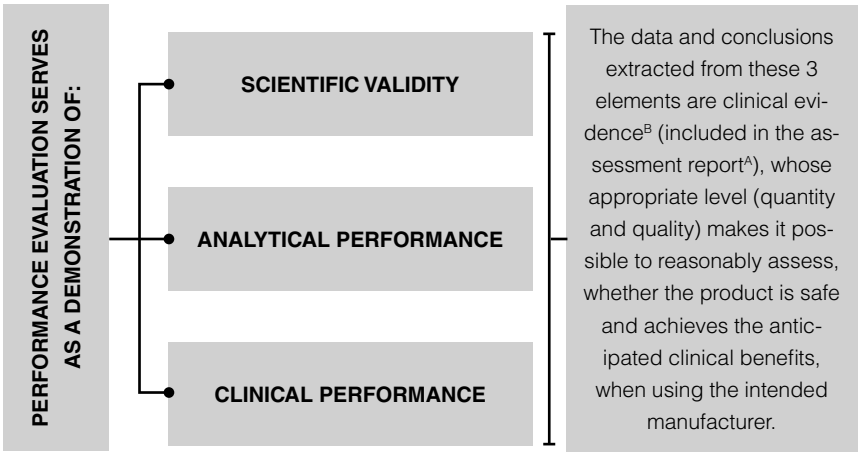
ate and appropriate to the characteristics of the device including the risks, risk class, performance and its intended purpose.

Clinical performance studies shall be performed unless it is justified why a demonstration based on other sources of clinical data is sufficient.

IVDR QUOTE:

Performance evaluation of a device is a continuous process, by which data is assessed and analysed to demonstrate the scientific validity, analytical performance and clinical performance of that device for its intended purpose, as stated by the manufacturer.

Figure 24: Main goals of performance evaluation



Sources: IVDR

KEY

A. The performance evaluation report is an important element of the safety and performance summary, and consequently the technical documentation. For devices of class C and D (products with relatively high risk), the update of this report is conducted if necessary, at least once a year, while the safety and performance summary is updated when necessary, as soon as possible.

B. Clinical evidence is obtained on the basis of demonstrating scientific validity, analytical performance and clinical performance, below we provide the content of the regulation and how to demonstrate it:

How to demonstrate scientific validity, analytical performance and clinical performance?

IVDR QUOTE:

a. ***Demonstration of the scientific validity***

The manufacturer shall demonstrate the scientific validity based on one or a combination of the following sources:

- *relevant information on the scientific validity of devices measuring the same analyte or marker;*
- *scientific (peer-reviewed) literature;*
- *consensus expert opinions/positions from relevant professional associations;*
- *results from the proof of concept studies;*
- *results from clinical performance studies.*

The scientific validity of the analyte or marker shall be demonstrated and documented in the scientific validity report.

b. ***Demonstration of analtycial performance***

The manufacturer shall demonstrate the analytical performance of the device in relation to all the parameters described in point (a) of Section 9.1 of Annex I, unless any omission can be justified as not applicable. As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies.

Analytical performance shall be demonstrated and documented in the analytical performance report.

c. ***Demonstration of the clinical performance***

The manufacturer shall demonstrate the clinical performance of the device in relation to all the parameters described in point (b) of Section 9.1. of Annex I, unless any omission can be justified as not applicable.

Demonstration of the clinical performance of a device shall be based on one or a combination of the following sources: clinical performance studies, scientific peer-reviewed literature, published experience gained by routine diagnostic testing.

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

Clinical performance shall be demonstrated and documented in the clinical performance report.

The purpose of clinical performance studies is to establish or confirm aspects of device performance which cannot be determined by analytical performance studies,

literature and/or previous experience gained by routine diagnostic testing. This information is used to demonstrate compliance with the relevant general safety and performance requirements with respect to clinical performance. When clinical performance studies are conducted, the data obtained shall be used in the performance evaluation process and be part of the clinical evidence for the device (Annex XIII, Section 2).

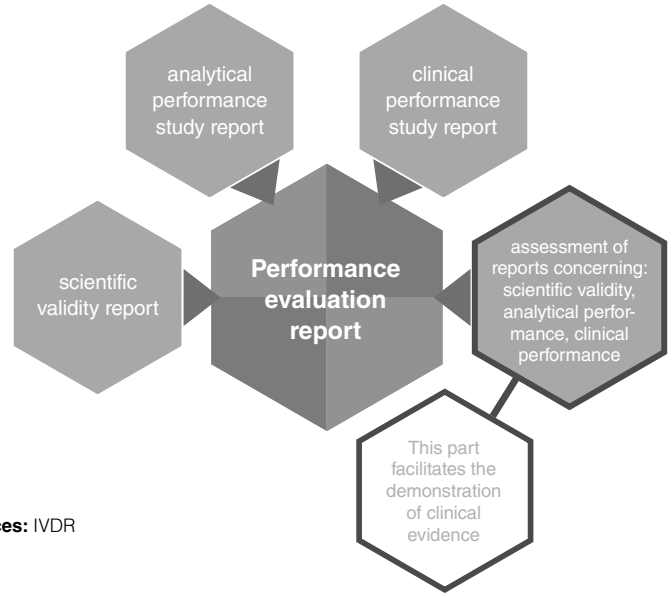
Documentation:

Figure 25: Documentation related to performance evaluation

What is needed to conduct a performance evaluation?	What is the result of a performance evaluation?
• performance evaluation plan • study reports of performance studies	• a performance evaluation report (structure according to fig. 26) – the data and conclusions drawn from this assessment constitute the **clinical evidence** for the device

The output of the performance evaluation is the performance evaluation report, its structure introduced below:

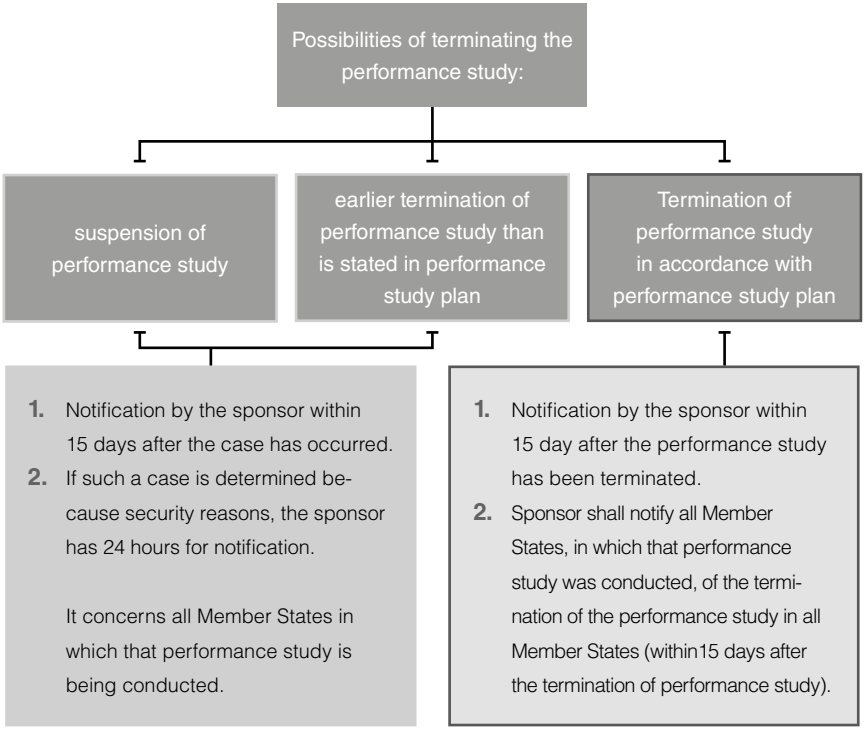
Figure 26: Structure of performance evaluation report:



Sources: IVDR

Regardless of the result of the performance study, the sponsor is required to submit the results of the performance study to the Member States in the performance study report (annex XIII, part A, section 2.3.3). Each of the three options for the termination of a performance study (fig. 27) results in such a report. In addition to the report, the sponsor submits a summary in such a way, that it is easily understandable for the intended user.

Figure 27: Paths of termination of a performance study



Sources: IVDR

Sponsors notify Member States through the electronic system concerning performance studies (part of Eudamed system). Regardless of the result of the study, in the case where the end of the performance study is as planned, the sponsor shall submit to the Member States where the performance study was conducted with a **performance study report** within a year; in 2 other cases (earlier termination and suspension), the sponsor shall complete this obligation

within **3 months**. Together with the report, the sponsor submits a summary prepared in such a way that it is easily understood by the intended user. It may also happen that for scientific reasons it will not be possible to submit a report within one year of the end of the study. The report shall then be submitted as soon as it becomes available. In that case, in the clinical performance study plan (annex XIII, part A, section 2.3.2), it shall be determined, when the results of the performance study will be available (together with justification).

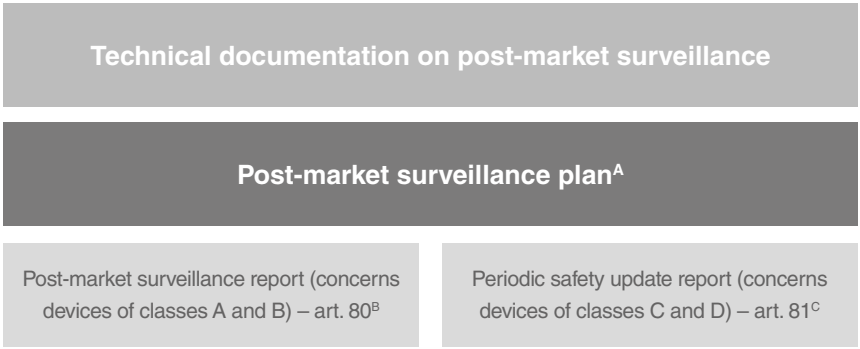
The report shall become publicly accessible in the electronic system (EUDAMED), no later than at the time of registration of the device, in accordance with article 26, and before it is placed on the market.

Additionally, for class C and D devices, other than devices for performance studies, the manufacturer shall prepare a **safety and performance summary**, what shall be part of documentation submitted to the notified body involved in the conformity assessment, and shall be made available to the public via EUDAMED (detailed information in article 29 of the IVDR).

4.3 Technical documentation on post-market surveillance

Post-market surveillance is an indispensable element for ensuring the safety of end users throughout the entire life cycle of the IVD biomarker product. In this sub-chapter, there is information regarding technical documentation on post-market surveillance, which should be completed simultaneously with the technical documentation.

Figure 28: Technical documentation on post-market surveillance system-structure



Sources: IVDR

KEY

A. The post-market surveillance plan is a part of the technical documentation (annex II), however, the maintenance and updating of the documentation is the obligation of the producer, which is required after the product has been placed on the market. The post-market surveillance plan is described in section 1 of annex III.

B. The report contains conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan and includes a rationale and the description of any preventive and corrective actions taken. The report shall be updated when necessary and made available to the notified body and the competent authority upon request.

C. PSUR play the similar role as post-market surveillance report. Throughout the lifetime of the device concerned, that PSUR shall set out: the conclusions of the benefit-risk determination, the main findings of the PMPF and the volume of sales of the device and an estimate of the size and other characteristics of the population using the device and, where practicable, the usage frequency of the device.

NOTE

Technical documentation on post-market surveillance can be planned and developed (at a certain level) simultaneously with creating an internal quality management system for an IVD biomarker product, which is a binding element between the parts of the full technical documentation.

This part of the documentation is based on a post-market surveillance system, that is an integral part of the quality management system. The post-market surveillance plan is an evidence of compliance with requirement of introducing a post-market surveillance system.

IVDR QUOTE:

The post-market surveillance system must be suitable for actively and systematically collecting, recording and analysing relevant data on the quality, performance and safety of the product over its entire lifetime, extracting the necessary conclusions and determining, implementing and monitoring any preventive and corrective actions.

After completion of the full technical documentation, the manufacturer can begin to prepare to conduct the conformity assessment, which will allow to obtain

the necessary certificates, as one of the requirements to be fulfilled before an IVD biomarker product can reach the market.

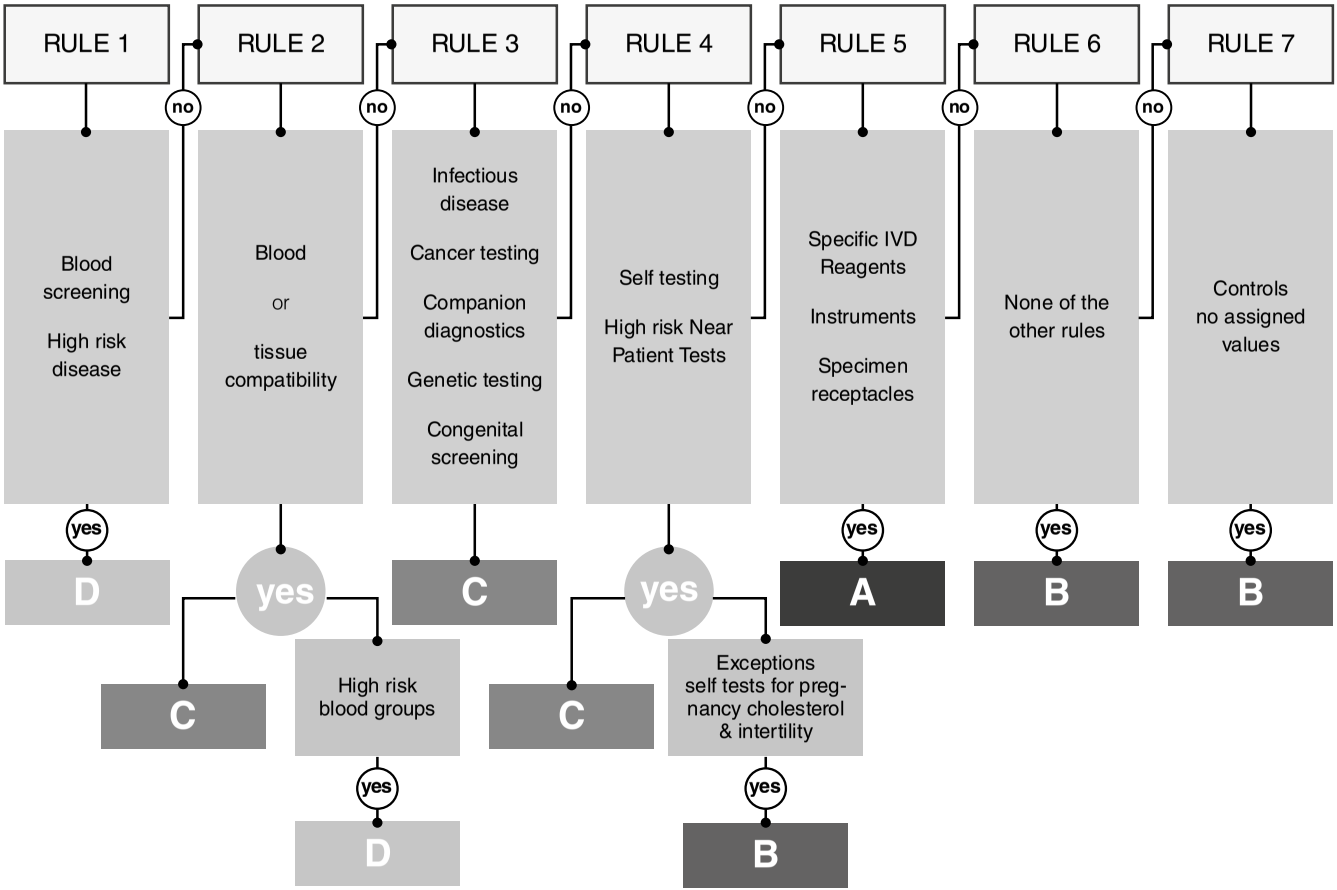
4.4 Conformity assessment procedure path related to the classification of relevant IVD medical devices

Each course of the conformity assessment procedure of a medical device for in vitro diagnostics depends on the classification of the product in a given risk group (A, B, C, D) and in a given generic device group. For this reason, in this chapter, the group classification of medical devices for in vitro diagnostics and dependences of individual conformity assessment procedures in relation to the affiliation of a product to a given group, are presented. In sub-chapters on specific product classes, (from 4.4.3 to 4.4.6), specific information for a given class of products has been included. **A device, for which the conformity assessment procedure has not been applied, cannot be placed on the market or used.** For the interest of public health or patient safety or health, competent authorities may, however, authorise use of a device in a EU member state as an exception to this rule in accordance with art. 54 of the IVDR (Derogation from the conformity assessment procedures).

4.4.1 IVD MEDICAL DEVICE CLASSIFICATION RULES

The classification of an IVD biomarker product is a manufacturer obligation and should be conducted according to article 47 & annex VIII of the IVDR. Affiliation to the relevant risk class of IVD medical devices determines the pathway, which has to be taken for the conformity assessment of an IVD medical device.

Figure 29: IVD medical classification acc. to Annex VIII IVDR rules



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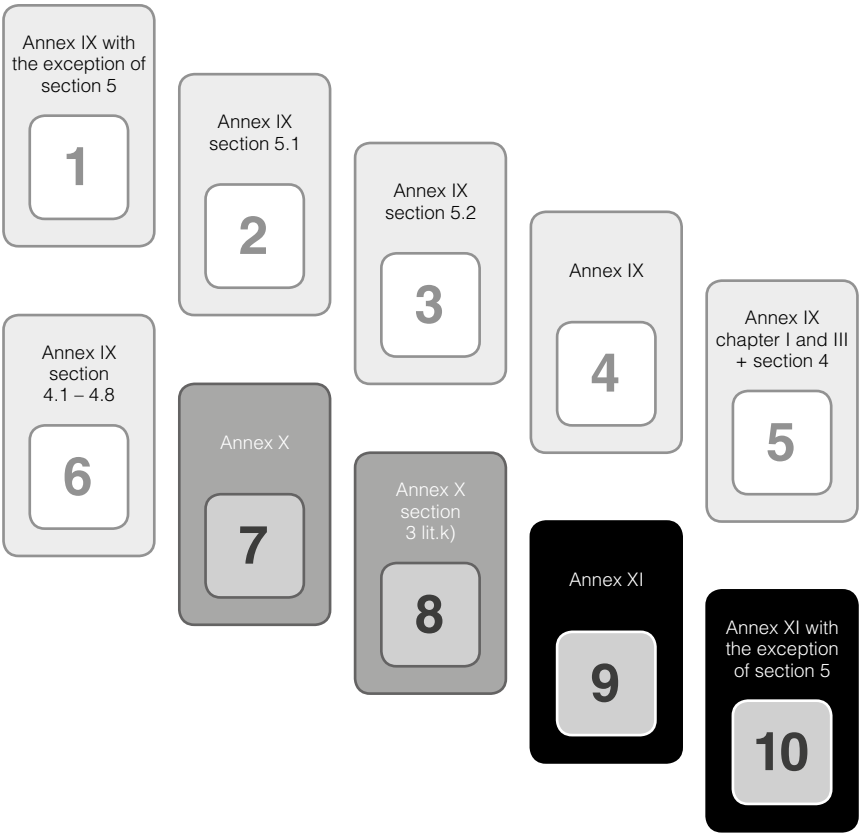
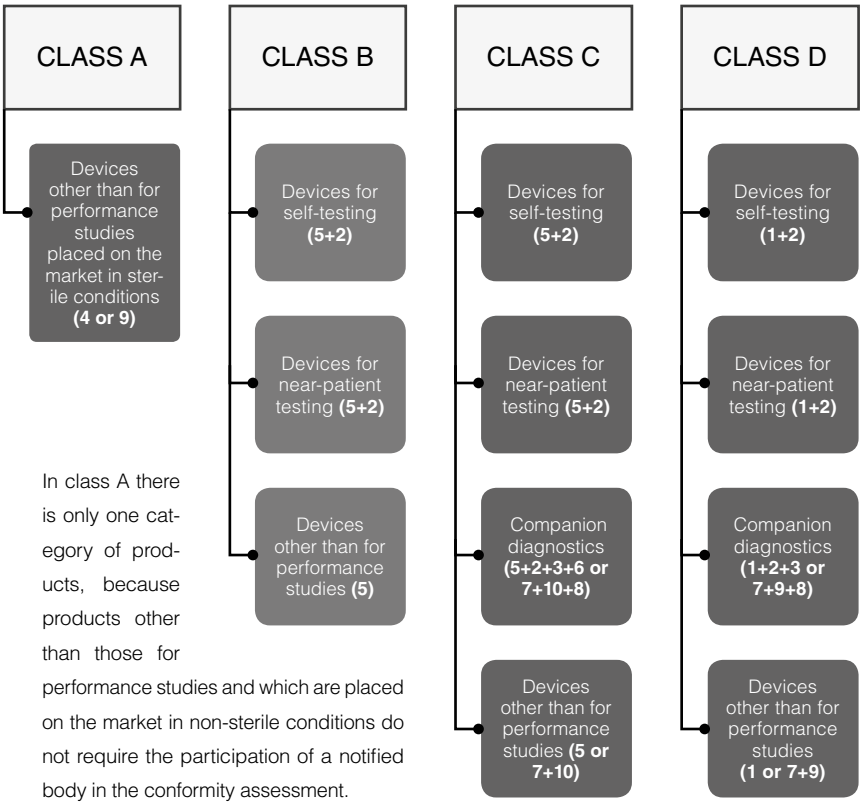
4.4.2 COURSE OF CONFORMITY ASSESSMENT PROCEDURE FOR EVERY GROUP AND CATEGORY OF PRODUCTS

Figure 30: Course of conformity assessment procedure for every group and category of products

Elements of conformity assessment procedures (equivalent to these elements are the numbers given in the brackets of the specific group of product which, aggregated, constitute a complete conformity assessment procedure) for all classes and product categories (in accordance with article 48):



Individual product categories (requiring the participation of a notified body to pass conformity assessment) divided into risk classes and the elements of conformity procedures assigned to them, as relevant:



In class A there is only one category of products, because products other than those for performance studies and which are placed on the market in non-sterile conditions do not require the participation of a notified body in the conformity assessment.

Sources: IVDR

KEY:

Certain product categories / types may be subject to two conformity assessment procedures (interchangeably). Each pathway of conformity assessment procedure can be considered as consists of relevant elements, that together define the review area. Elements of procedures have been coded numerically. It is advisable to consider annex IX as the default conformity assessment option.

ANNEX IX: Conformity assessment based on a quality management system and evaluation of technical documentation – a successfully passed procedure results in the obtainment of a EU quality management system certificate and an EU technical documentation assessment certificate.

ANNEX X: Conformity assessment based on type-examination – A successfully passed procedure results in the obtainment of a EU type-examination certificate.

ANNEX XI: Conformity assessment based on production quality assurance – A successfully passed procedure results in the obtainment of a EU production quality assurance certificate.

Relations between conformity assessment procedures of different categories and classes of devices:

a. By coding relevant conformity assessment procedures using colours, it can be easily demonstrated that all devices (regardless of class) shall be certificated by conformity assessment procedures based on the quality management system and the evaluation of technical documentation marked in **light grey (according to annex IX of the Regulation)**. If there is an alternative in the form of a second certification course for the relevant device, then the full procedure (alternative procedure) consists of 2 conformity assessment procedures in the appropriate configurations: conformity assessment based on type-examination – **grey (annex X of the Regulation)** and conformity assessment based on production quality assurance in **black (annex XI of the Regulation)**.

b. Products whose compliance with the requirements can be justified in 2 ways are:
   - in C class: devices other than for performance study and companion diagnostics (devices for self-testing and devices for near-patient testing are exempted)
   - in D class: devices other than for performance study and companion diagnostics (devices for self-testing and devices for near-patient testing are exempted)

c. devices for near-patient testing and devices for self-testing within one class of risk are certified by the same conformity assessment procedures, moreover:
   - devices for near-patient testing of C and D classes are certified by the same conformity assessment procedures
   - devices for self-testing of C and D classes are certified by the same conformity assessment procedures

Each successful conformity assessment procedure with the participation of a notified body, is finalized by obtaining of a EU certificate of conformity (each certificate is assigned to one conformity assessment procedure, so the procedure in accordance with **annex IX of the Regulation** consists of two separate certificates).

IVDR QUOTE:

EU certificates of conformity *issued by a notified body are* ***valid*** *for the period, indicate on the certificate, of a* ***maximum 5 years****. Certificates may be renewed upon application by the manufacturer for additional max. 5 years subject to re-assessment by the notified body. Certificates shall be determined in an EU official language by the Member State in which the notified body has been established. The minimum content of certificates is described in Annex XII of the IVDR.*

Detailed information (content, scope, etc.) about EU certificates of conformity can be found in annex XII.

4.4.3 CLASS A-ADDITIONAL INFORMATION

For IVDR Class A devices, an assessment by a notified body is not required. For all other classes the notified body audit is part of the conformity assessment procedure. Notice that if the product belongs to category IVDR A (s) (sterile) these properties require an assessment by a notified body.

Further guidance on class I devices can be found in annex VIII and MDCG 2020-16 Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746.

4.4.4 CLASS B-ADDITIONAL INFORMATION

Devices of B class are not burdened by additional compliance verification and performance declarations. Operation in accordance with the standard conformity assessment procedure (and fulfilment of additional requirements) for B class devices is sufficient enough to be able to place products on the market (according to figure 30 of Regulatory Guide).

4.4.5 CLASS C-ADDITIONAL INFORMATION

At the request of a Member State, devices of C class shall be additionally verified in the field of compliance with Regulation and declared performance (conducted by the designated EU reference laboratory (article 100)), in accordance with the procedure (annex IX, chapter II, section 4.9). Surveillance assessment is also applicable to devices of C class (annex IX, chapter I, section 3).

Additionally, for class C devices, other than devices for performance studies, the manufacturer shall prepare a **safety and performance summary** which will be part of the documentation submitted to the notified body involved in the conformity assessment and shall be made available to the public via Eudamed (detailed information in article 29 of the IVDR).

4.4.6 CLASS D-ADDITIONAL INFORMATION

When analysing the conformity assessment procedures of D class devices, it should be emphasized that these devices are controlled in the most rigorous of all product classes. They are **additionally** verified on the declared performance and compliance with the common specifications under the conformity assessment procedure (annex IX, chapter II, section 4.9 of the IVDR) conducted by a EU reference laboratory at the request of a notified body.

Before issuing the certificate, the notified body, who is conducting the conformity assessment, requests the EU reference laboratory for verification of the declared performance by the manufacturer and compliance of the product with the relevant requirements of the IVDR. This verification includes laboratory tests conducted by the EU laboratory (referred to in article 48 paragraph 5 of the IVDR). The producer provides samples of manufactured batches of the product under the pre-determined conditions.

In the case, that common specifications for devices of D class are not available, and this is the first certification of such products, the notified body consults with relevant experts, in accordance with the procedure set out in art. 48 par. 6 of the IVDR

Surveillance assessment is also applicable to devices of D class (annex IX, chapter I, Section 3 of the IVDR).

In order to verify the compliance (with IVDR) of the manufactured D class devices, the manufacturer must conducted tests on each batch of the products manufactured, forward test reports to the notified body in addition to provide batch samples available for independent testing at EU reference laboratory.

Additionally, for class D devices, other than devices for performance studies, the manufacturer shall prepare a **safety and performance summary**, which will be part of the documentation submitted to the notified body involved in the conformity assessment and shall be made available to the public via Eudamed (detailed information in article 29 of IVDR).

4.4.7 FDA INFORMATION

In the United States, there are 3 key regulatory authorities which regulate diagnostics: Centres for Medicare and Medicaid Services (CMS), Federal Trade Commission (FTC) and the Food and Drug Administration (FDA). CMS regulates clinical labs, FTC regulates the advertising of devices, and FDA regulates test kits (IVD tests). The FDA operates on the basis of the Federal Food, Drug and Cosmetic Act and is comprised of numerous centres. A specific centre is responsible for a specific product regulated by the FDA, if concrete device is the matter of concern of more than one centre, relevant centres cooperate.

The FDA requirements for IVD products are considered more restrictive as those of the IVDR, therefore, a product developed under U.S. requirements will probably not have a problem in fulfilling the requirements of the European regulatory system for IVDs. The U.S. regulatory system categorises IVDs into three classes reflecting the level of risk and amount of regulation to comply with: Class I, Class II and Class III. Manufacturers should seriously consider market size before starting to develop a product adjusted to a specific regulatory pathway.

It is worth noting, that the most significant similarity between the FDA and IVDR requirements is that both systems categorise IVDs according to risk, and the classification within classes determines the level of regulation for a device. The FDA (through the FD&C), as well as the IVDR, require evidence supporting the intended use and indication for a test. Both regulatory systems assume post-market responsibilities.

However, the elaboration on the U.S. IVD regulatory system and its comparison to the European regulatory framework is not an aim of this document. FDA elaborated material providing comprehensive knowledge about the U.S. IVD regulatory system, includes laboratory standards via CLIA. Comprehensive standards in quality control of laboratory processes, requirements for technicians and proficiency are provided by CLIA regulation prepared by CMS. **However, it needs to be emphasized that this regulation is not obligatory in the EU.**

More information can be found on the FDA website. To get an overview of it is worth, start here:

https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation

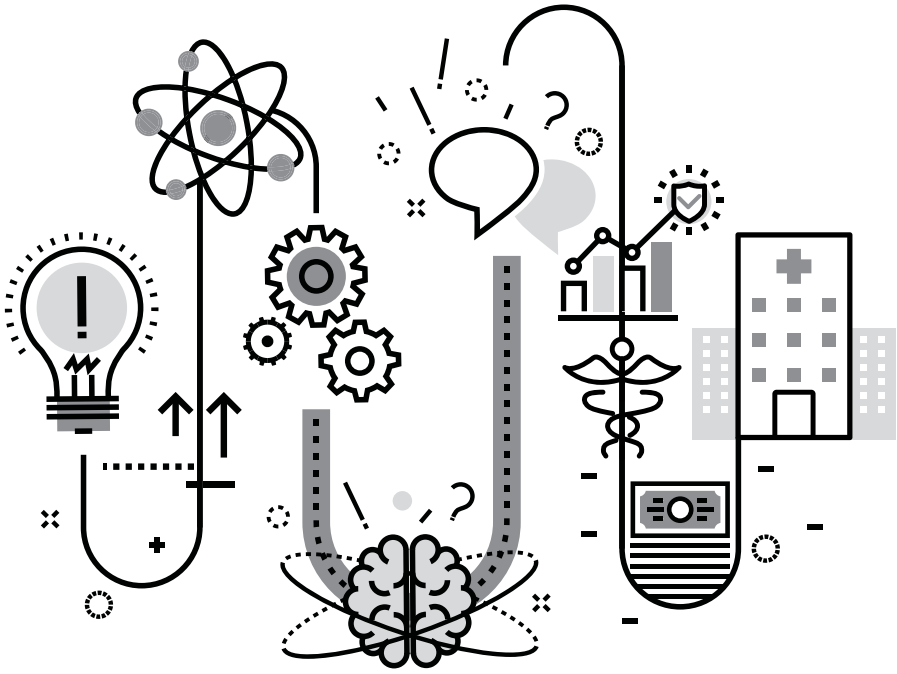
Other links:

https://www.fda.gov/medical-devices/products-and-medical-procedures/vitro-diagnostics

https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia

https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products

5
SUMMARY



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The commercialization of IVD medical devices is long, laborious (multi-staged, cumbersome) and requires the participation and cooperation of many entities. The progression from science to business enabled the commercialization of many medical devices and opened new areas of diagnostics and treatment. Therefore, it is necessary to carefully balance scientific and business requirements to leverage the full potential of biomarkers for disease prevention, diagnosis and monitoring. Diagnostics is still a dynamically developing and yet underexploited sector of the global healthcare economy.

The commercialization of biomarkers presents many challenges. In view of the multi-stage development process with the participation of stakeholders of many disciplines and other external entities, developing biomarker discoveries into IVD medical devices and placing these on the market is very demanding. It requires efficient cooperation between BCVC stakeholders, which must be able to answer each other's expectations and needs. The BIC project aims to make the development process more familiar to stakeholders and easier to pass through. The tools developed within the BIC project should contribute to the improvement of knowledge among the BCVC stakeholders and encourage them to commercialization.

The EU regulatory system for IVDs is currently in a state of flux, therefore amendments to the regulation, release of delegating and implementing acts, new MDCG guidances, harmonised standards and common specification are expected in the future, and as a result, the BIC Regulatory Guide will require updating with these changes.

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FAQ (FREQUENTLY ASKED QUESTIONS)

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1. **Can two different conformity assessment procedures be carried out simultaneously?**
   It is not possible to carry out two different conformity assessment procedures concluded with the issuing of a certificate simultaneously for the same product.

2. **Can technical documentation on post-market surveillance not be prepared simultaneously with the technical documentation?**
   The technical documentation shall contain the elements set out in annexes II and III of the IVDR. The technical documentation on the post-market surveillance as set out in annex III, with the exception of the periodic safety report and the post-market surveillance report, should be prepared simultaneously with the technical documentation set out in annex II to the Regulation.

3. **Are conformity assessment certificates sufficient to place a product on the market?**
   According to article 5(1): a device may be placed on the market or put into service only if it complies with this Regulation when duly supplied and properly installed, maintained and used in accordance with its intended purpose. Certificates of conformity are one of the requirements set by binding law, but are not enough in itself to place a product on the market. "Further requirements are the registration of economic operators and devices with the database (EUDAMED)"

4. **What are the differences between individual conformity assessment procedures? For what purpose is it possible to choose a "path" of conformity assessment procedure for an individual product?**
   The choice of the conformity assessment procedure depends on the manufacturer, who may use the possibilities set out in the Regulation for a given product. This choice can be dictated by many factors, first of all, the scope of the quality management system and the cost of a given conformity assessment procedure can be taken into account. For example, manufacturers of class D products (other than devices for performance study) shall be subject to the conformity assessment set out in chapter I of chapter II of annex IX, with the exception of section 5 (if applicable) and chapter III, or they may use the conformity assessment set out in annex X in combination with the conformity assessment set out in annex XI.

5. **Is permission to conduct a performance study always required?**
   Participants taking part in the product performance study will be subjected to an *in vitro* test with a device for performance studying. On the other hand, a performance study can also be carried out using the remains of samples after routine patient examinations. In this case, a performance study using residual samples does not have to be subject to the obligation of obtaining a permit. Nevertheless, general and other additional data protection requirements and requirements applicable to procedures implemented in accordance with national rules, such as ethical approval, should continue to apply to all performance studies, including those using sample residues.

6. **Can conformity assessment procedures be carried out when the technical documentation is incomplete?**
   According to art. 10(4) of the IVDR, technical documentation is prepared in such a way as to enable the conducting of a conformity assessment of a product in compliance with the requirements of this Regulation. Conformity assessment, in order to avoid complications, should be carried out when the technical documentation of a relevant product fulfil IVDR requirements and enable the obtainment of certificates.

7. **How long does the standard process of in vitro diagnostic medical device commercialization take?**
   IVD assay is able to reach the market within 1-3 years depending on the risk class of the IVD medical device.

More FAQs (gained and devised by CAMD) can be found here:

https://www.camd-europe.eu/regulatory/available-now-mdr-ivdr-transitional-faqs/

and (devised by European Commission) here:

https://ec.europa.eu/docsroom/documents/33622

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WROCLAW TECHNOLOGY PARK

AALBORG UNIVERSITY HOSPITAL

Technical, regulatory, and business considerations form the three corner stones of biomarker commercialization. A general understanding of regulatory issues is recommended for all stakeholders and should be taken into consideration from the very beginning of the biomarker development process.

The IVDR Guide provide a comprehensive introduction to the in-vitro diagnostics regulation (IVDR) for researchers and SMEs that are taking the first dives into this topic. It introduces researchers and entrepreneurs to basic understanding of the regulatory process for CE mark of IVD diagnostics, along with the development of the project toward a clinical product.

This Guide includes information on:

- how to approach regulatory affairs,
- planning of IVDR implementation,
- management of regulatory aspects of commercialization,
- positioning the regulatory obligations within relevant commercialization stages, taking into account aspects of time and maturity of the biomarker project,
- introducing good practices related to regulatory field.

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