In vitro diagnostics

BIC Regulatory Guide

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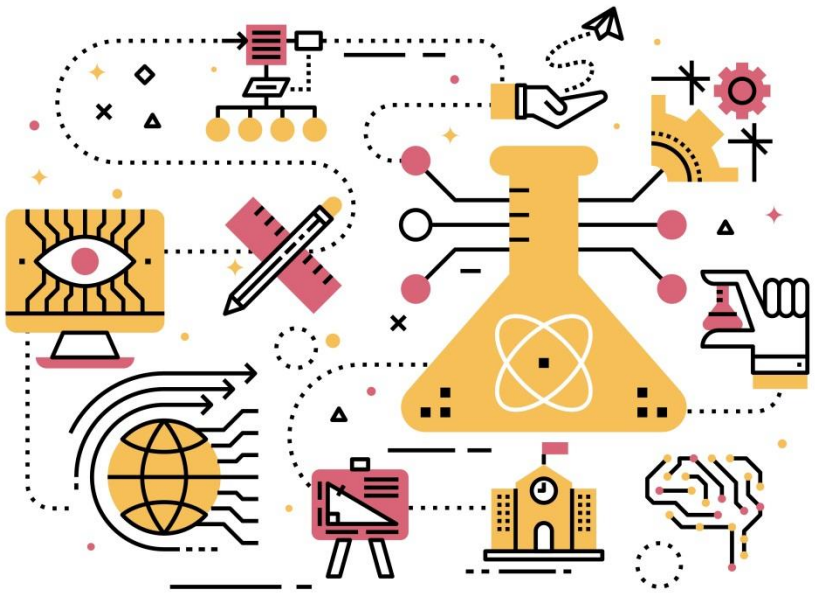

Imprint

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.

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Contents

1.Introduction

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 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 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

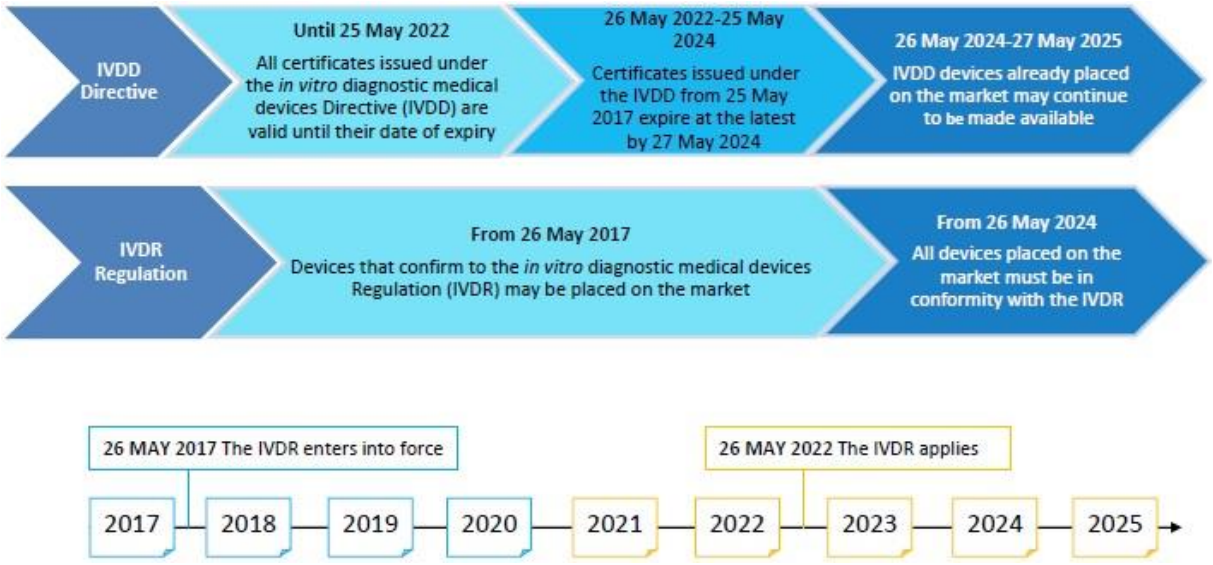
Regulatory issues in the IVD biomarker commercialization field have been introduced in respect to the commercialization model proposed by the BIC consortium. The substantive content was based on Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices ('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 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=CELEX: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 Requirement(s);

"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 guide 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

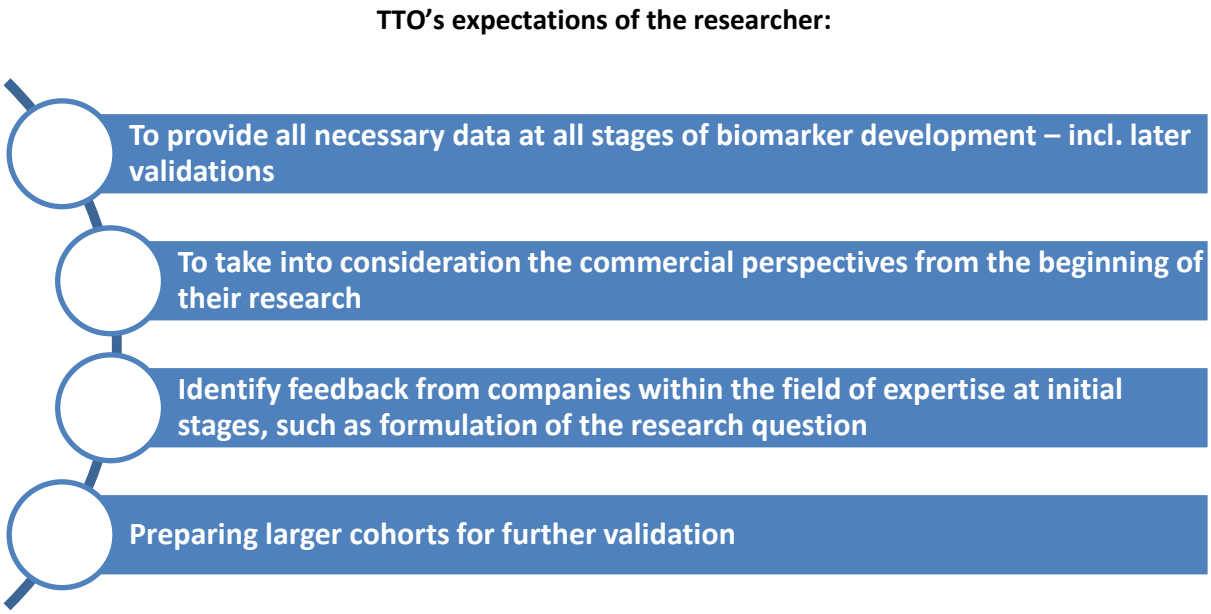
2.1. General involvement of stakeholders in the biomarker commercialization value chain

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 most predominant path currently recognised (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 leads 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).

Figure 2: TTOs expectations



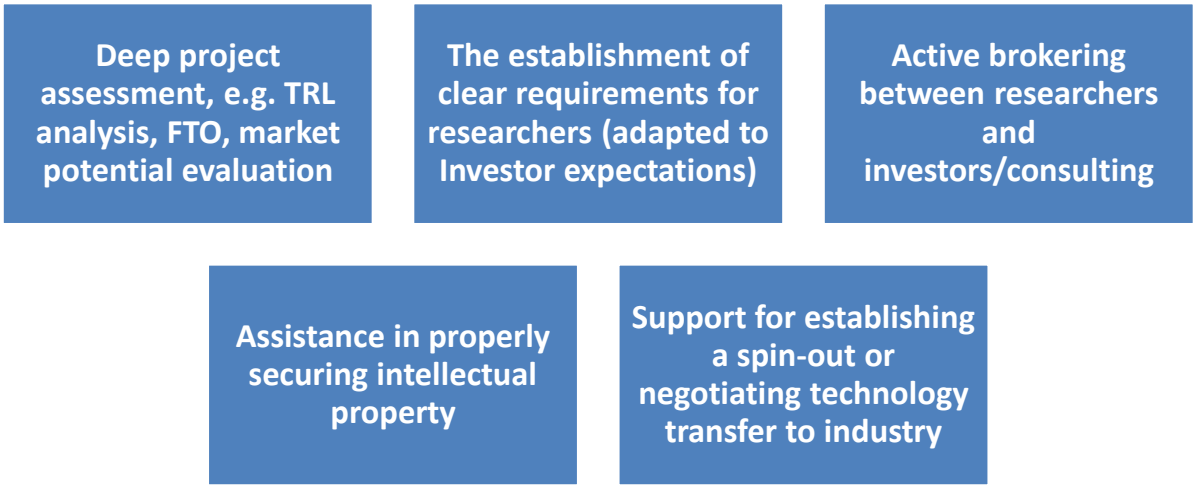
Sources: BIC interviews

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

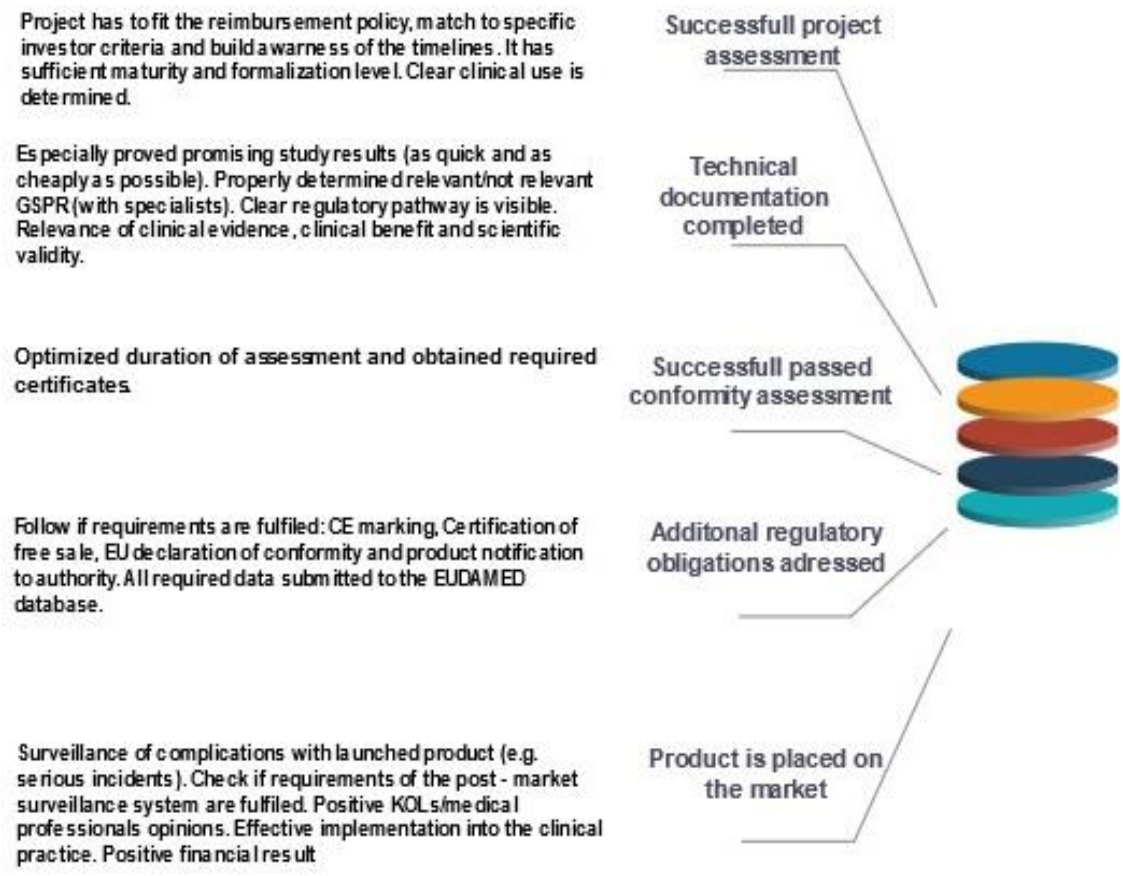
Investors usually remain solely as resource donors, mostly interested in commercial value of final product and clinical benefit associated with it rather than in scientific value of it (business approach). As resource providers, **they do not face regulatory issues themselves**. The EU IVDR is not applicable 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 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 (fig. 4) below. 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:

1. Identify KOLs using a scientific approach
2. Clearly outline the needs of the KOL and your company
3. Keep track of KOL engagement with your company
4. Remember that collaboration with KOLs is a two-way street that may involve the sharing of sensitive data
5. 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.

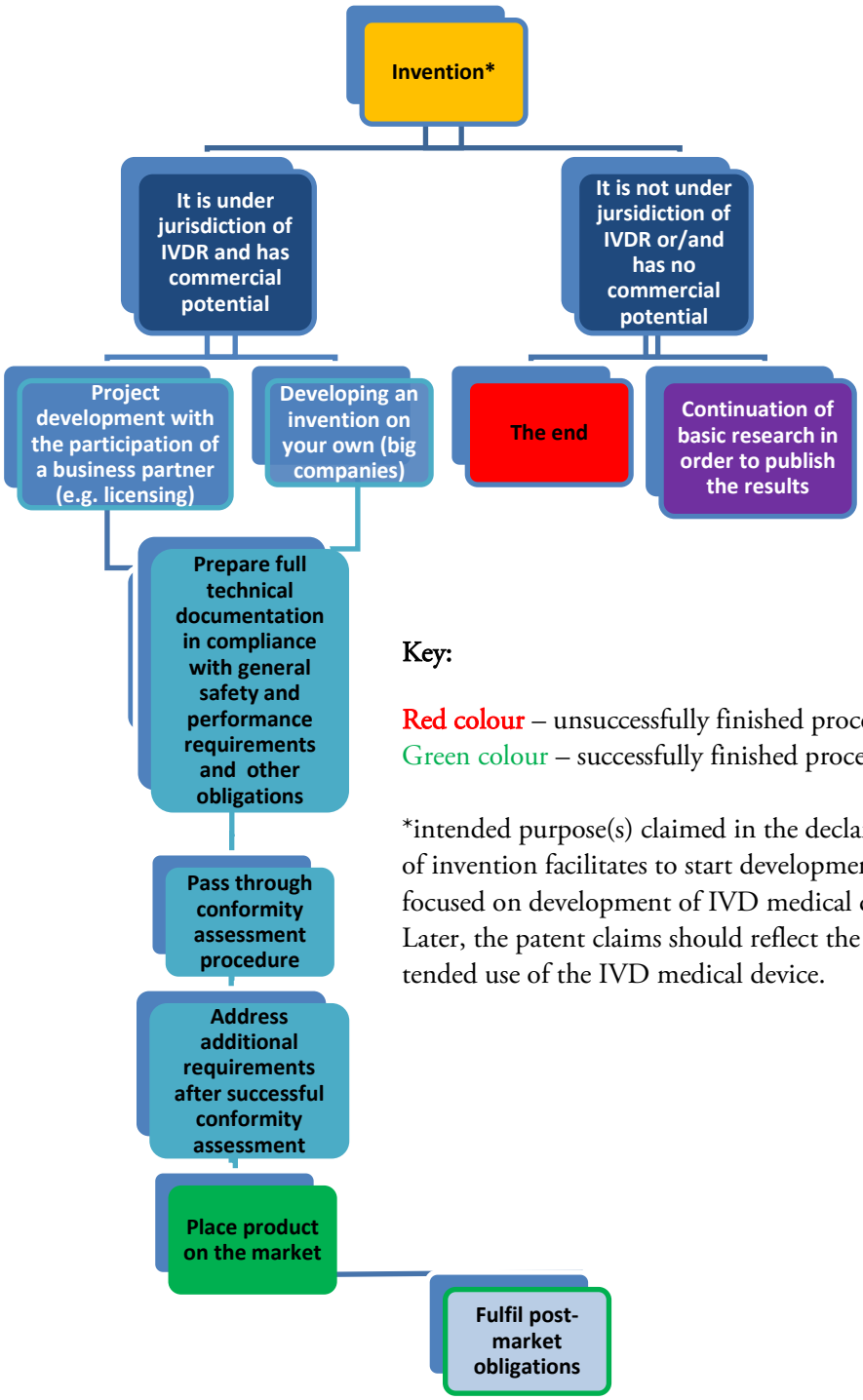
Regulation is designed to ensure the safety of the end-user and patient. Only the intended use of the device as specified by the manufacturer determines the end-user, e.g. near-patient testing device - clinical end-user. End-users should also be enabled to report serious incidents at a national level (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

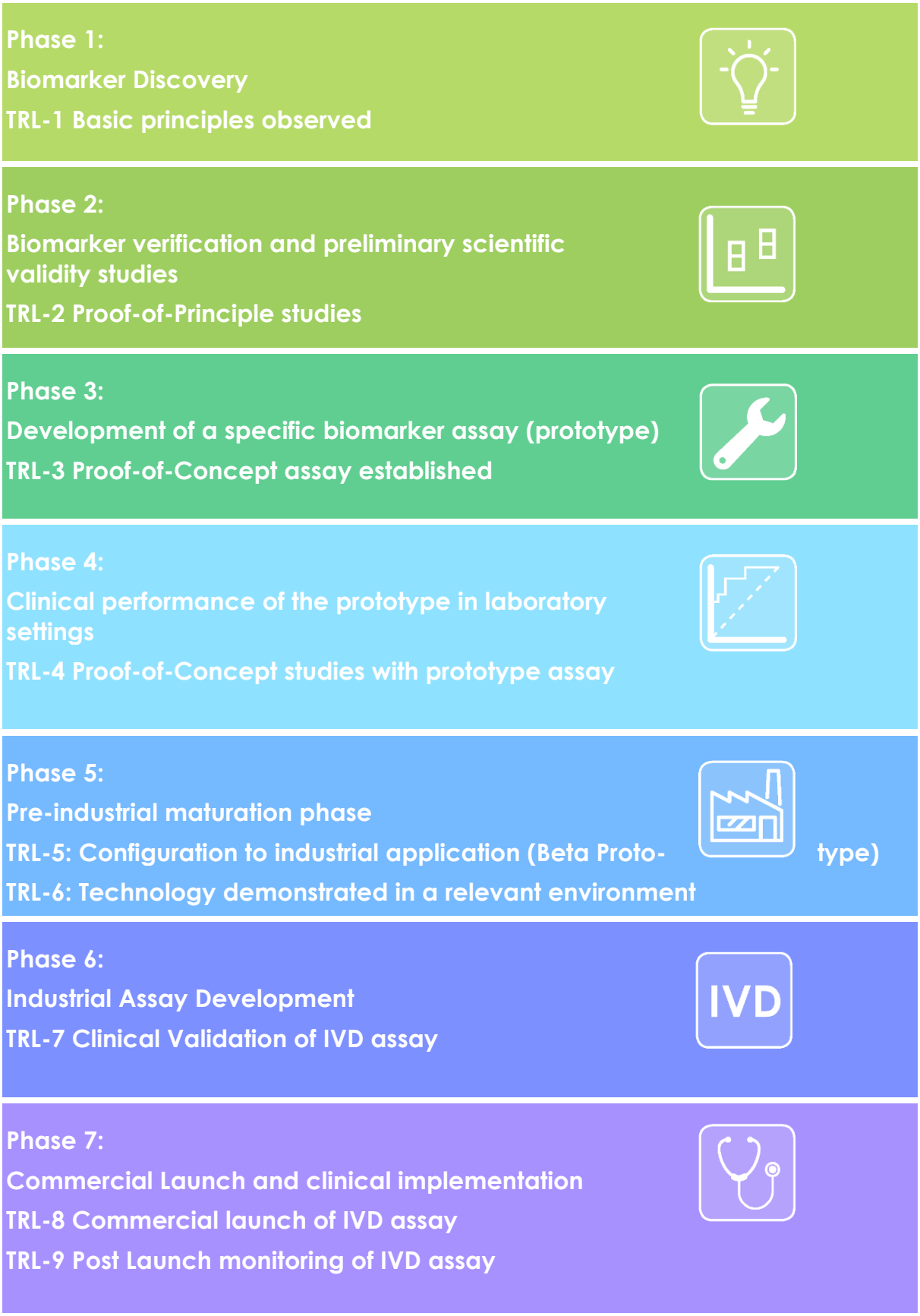
Figure 5: Biomarker assay commercialization process from regulatory point of view (on the basis of IVDR) – from invention to the market implementation - general scheme



3.Commercialization

in process approach

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



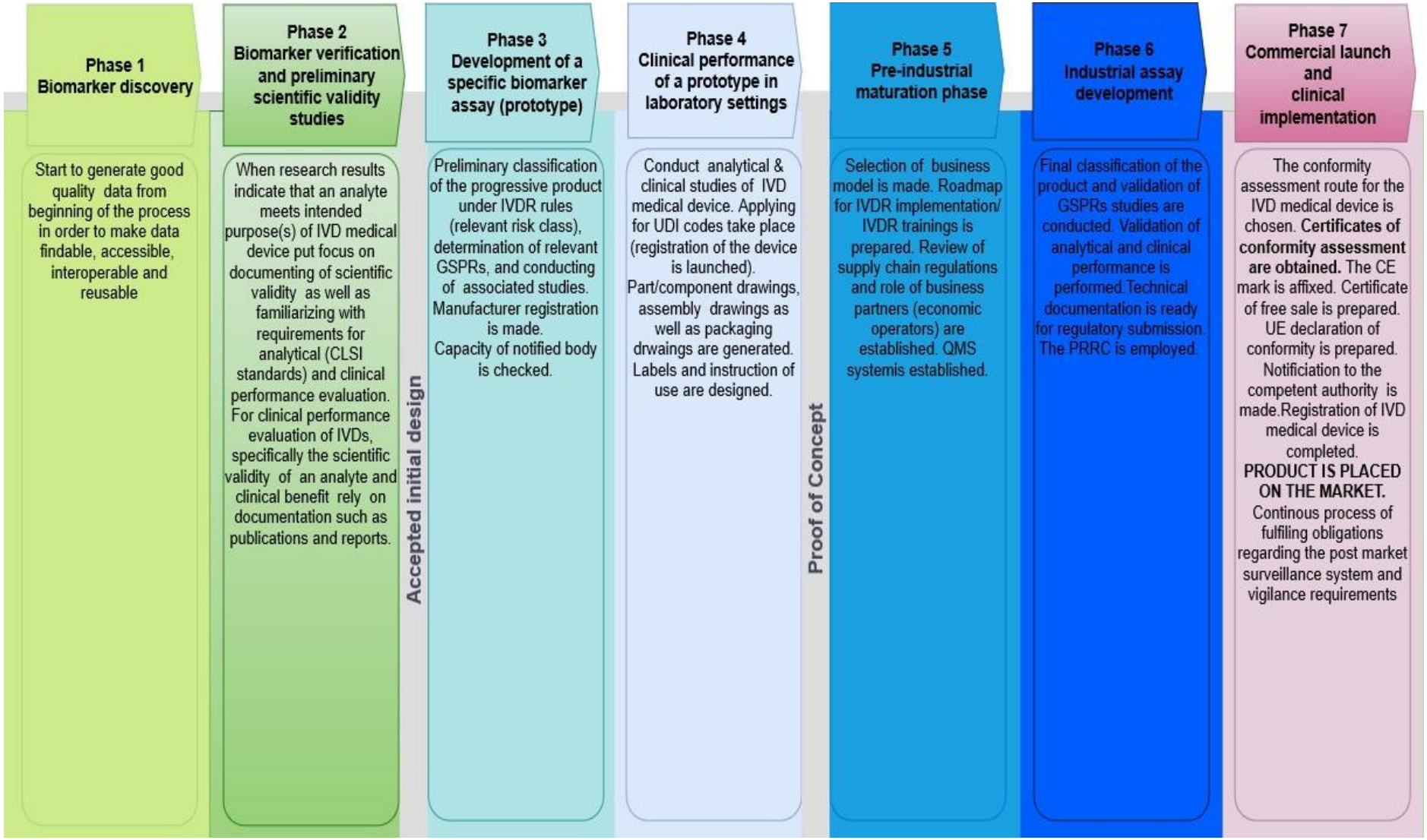
Sources: BIC project

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 covered.

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 phase specific tables, 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



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

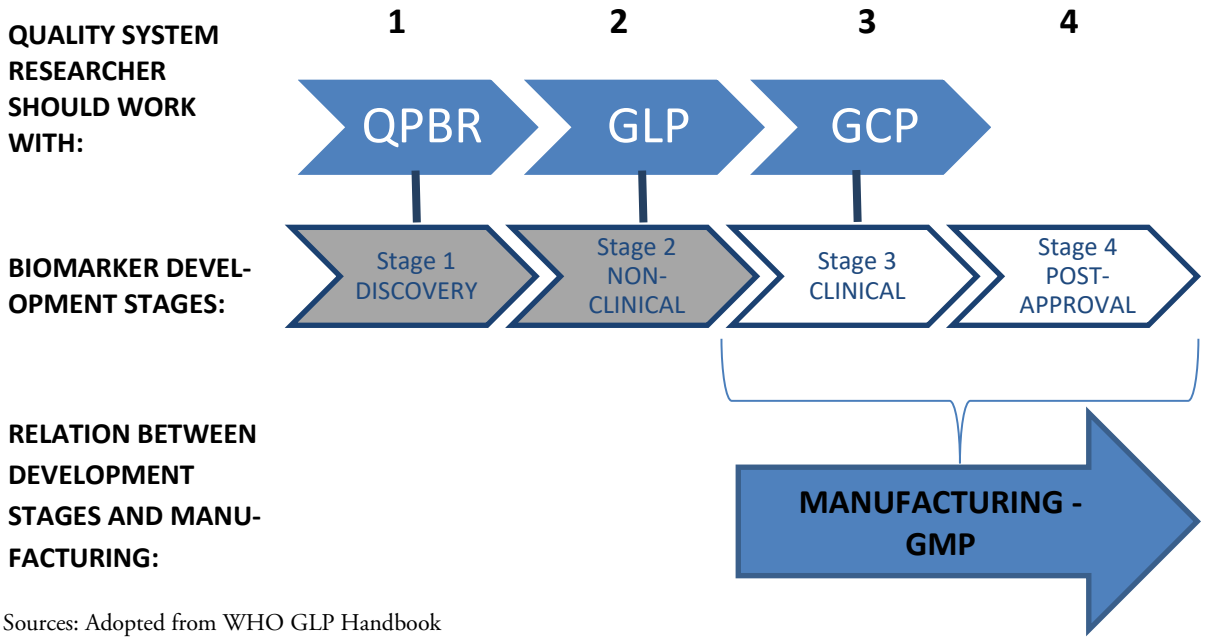
Sources: BIC interviews

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 facilitate 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 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 (coloured in grey) in biomarker development concerning the **researcher** (biomarker commercialization value chain member context).

Figure 10: Regulatory tasks regarding discovery phase

Regulatory tasks regarding discovery phase

Regulatory tasks to fulfil within 1st commercialization stage	Good practices
❖ **Familiarise with general information regarding the early stages of development from a regulatory perspective** The stages of the IVD assay commercialization process that do not forecast the participation of enterprise (at the early stages of development) do not contain mandatory regulatory tasks regarding product placement on the market (required by IVDR). The researcher has to take into account a regulatory pathway that biomarker products have to go through, but he/she is not legally responsible for it. Therefore, tasks concerning regulatory aspects at the early stages were developed on the basis of good practices. Application of the practices would potentially improve the pace of industry assay development (fulfil legal enterprise obligations), and as a result place the product on the market. Link to IVDR: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0746 ❖ **Consideration for ethical approval for the use of biological material** Currently, the European legal framework for the use of biological material and biobanking does not exist, and national regulations may vary from country to country. 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 transnational exchange of samples - if yes, additional requirements	❖ **Plan how you will compile your data and results** From a regulatory point of view, the researcher, from the beginning of the biomarker project, is responsible for collecting good quality and relevant data (input for technical documentation). Well-structured raw data and availability, facilitate further comparisons, validation and reduce differences in re-tests. Research should be carry out in conformity with current standards and IVD methods. It's recommended to implement quality system and/or data management & stewardship system, e.g. GLP, FAIR. ❖ **Work according to a quality system for non-clinical studies & familiarise with the "state of the art" of IVD development** Be familiar with the popular standards: QPBR, GLP, FAIR (for scientific data management and stewardship). Consider if there are any specific rules that require the use of a system. GLP handbook by WHO can be found here: https://www.who.int/tdr/publications/documents/glp-handbook.pdf 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

may arise. ❖ **Considerations 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.	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
ACHIEVEMENTS OF THE PHASE ARE IMPORTANT FROM A REGULATORY PERSPECTIVE: ETHICAL APPROVALS FOR RESEARCH	

Sources: IVDR, BIC resources

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.

Figure 11: Regulatory tasks regarding scientific preliminary validity of the biomarker

Regulatory tasks regarding biomarker verification and preliminary scientific validity studies	
Regulatory tasks to fulfil within the 2nd commercialization stage	Good practices
❖ **There are still no mandatory tasks to fulfil at this phase within IVDR, however preparation work as described under good practices should be initiated** The stage concerns biomarker lab research – no mandatory regulatory requirements to fulfil. **Reminder:** The stages of the IVD assay commercialization process that do not forecast the participation of enterprise (at the early stages of development) do not require mandatory regulatory tasks regarding product placement on the market (required by IVDR). The researcher has to take into account a regulatory pathway that biomarker products have to go through, but he/she is not legally responsible for it. Therefore, tasks concerning regulatory aspects at the early stages were developed on the basis of good practice. Application of the practices would potentially improve the pace of industry assay development (fulfil legal enterprise obligations), and as a result place the product on the market.	❖ Follow good practices from phase 1
ACHIEVEMENTS OF THE PHASE ARE IMPORTANT FROM A REGULATORY PERSPECTIVE: ACCEPTED INITIAL DESIGN OF AN ASSAY	

Sources: IVDR, BIC resources

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 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 bicguide.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)). Moreover, it is important to collect analytical performance data under the IVDR requirements in order to avoid further adjustments.

Figure 12: Regulatory tasks regarding development of a specific biomarker assay

Regulatory tasks regarding the development of a specific biomarker assay (prototype)	
Regulatory tasks to fulfil within the 3rd commercialization stage	**Good practices**
❖ **Registration of IVD medical device manufacturer** Apply article 26 & article 28; chapter 4.2.1 of RG Proceed through the registration procedure within the EUDAMED database.	❖ **Determine if the assay is under jurisdiction of EU IVDR** Apply Article 1, Article 2(2), Article 5(5) and if uncertainty exists, Article 3 of the IVDR. Is 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; - defining or monitoring therapeutic measures. ❖ **Collect data related to the analytical performance of the assay in respect to IVDR requirements** Analytical performance data has to meet specific criteria determined by the IVDR. Apply Annex I Chapter II (9.1)(a), (9.3.) and Annex II (6.1.)of the IVDR. During analytical (and clinical) performance studies, take into account IVDR requirements in that field. Well-structured raw data concerning specific characteristics is necessary to provide and constitute essential input for technical documentation further gathered by the entrepreneur. The analytical performance takes into account data characteristics, 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 the determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference and 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"

Link: http://www.imdrf.org/docs/ghtf/archived/sg1/technical-docs/ghtf-sg1-n063-2011-summary-technical-documentation-ivd-safety-conformity-110317.pdf

❖ **Collect data for justification of scientific validity of a progressing assay**

Apply Annex XIII, Part A, section 1.2.1

More information on how to justify the scientific validity of the IVD medical device can be found here (section 6 of linked document):

http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf

ACHIEVEMENTS OF THE PHASE ARE IMPORTANT FROM A REGULATORY PERSPECTIVE: BASIC INPUT FOR THE ANALYTICAL PORTION OF PRODUCT VERIFICATION AND VALIDATION

Sources: IVDR, BIC resources

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.

Figure 13: Regulatory tasks regarding prototype performance in laboratory settings

Regulatory tasks regarding prototype performance in laboratory settings

Regulatory tasks to fulfil within the 4th commercialization stage	Good practices
❖ **Obtain ethical approval for clinical studies.** Revise the appropriateness of previously obtained ethical approvals. Obtain ethical approval and patient consent for your clinical studies. Submit the application for clinical studies, and if approved, begin tests. Apply ISO 20916:2019 "In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practices". This ISO 20916 should be used also clinical performance studies under the IVDR. However, it has been recognised that some of the requirements set out in ISO 20916 are not fully aligned / harmonized with the IVDR and that further guidance to address the differences would be of benefit to industry and other stakeholders. Only the text of the IVDR is legally binding. In cases of divergence between the ISO 20916, the IVDR and any future MDCG guidance shall take precedence. ❖ **Applying for UDI codes of the IVD medical device** Apply article 24 & article 26 and start process of IVD medical device registration by applying for UDI codes. ❖ **Design labels and instructions of use according to annex I chapter 3** ❖ **Prepare part/component drawings, assembly drawings and packaging drawings.**	❖ **Submit the application for clinical studies according to figure 28 of RG and article 66** ❖ **Collect data related to clinical performance of the assay in respect to the IVDR requirements** Apply Annex I Chapter II (9) of the IVDR. During clinical (and analytical) performance studies, take into account 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. Follow the GHTF standards in clinical performance evaluation: GHTF/SG5/N8:2012 "Clinical evidence for IVD medical devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices and GHTF/SG5/N7:2012 "Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation" http://imdrf.org/documents/doc-ghtf-sg5.asp ❖ **Preliminary classification of the assay into risk classes of IVD** Apply article 47 and annex VIII. Follow figure 36 of RG. Initial determination of the risk class of the intended assay (A, B, C or D). Note that IVD biomarker applicable assays typically fall into classes C or D. Classification to the relevant risk class determines the regulatory pathway an assay has to go through. Preliminary classification could be expected by the business partner interested in the project in case of costs, time and efforts required to put IVD medical device on the market.

❖ **Preliminary establishment of relevant/irrelevant general safety & performance requirements according to the product characteristics and risk related to its use**

Apply annex I and annex III. Read chapter 4.1 of RG.

From a regulatory standpoint, it is crucial for IVD medical devices to determine performance specifications and product characteristics and manage risks (identify, analyze, estimate, evaluate or control risks) related to product performance, design and manufacture as soon as possible. After that, applicable general safety & performance requirements can be determined. It constitutes a significant input for further technical documentation of the product and determine the form of business partnership.

IMPORTANT ACHIEVEMENTS OF THE PHASE FROM A REGULATORY PERSPECTIVE: BASIC INPUT FOR THE CLINICAL PORTION OF PRODUCT VERIFICATION AND VALIDATION, INITIAL CLASSIFICATION OF THE PRODUCT, RELEVANT AND IRRELEVANT GSPRs ARE DETERMINED, PROOF OF CONCEPT

Sources: IVDR, BIC resources

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 **enterprise,** 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.

Figure 14: Regulatory tasks regarding the pre-industrial maturation phase

Regulatory tasks regarding the pre-industrial maturation phase	
Regulatory tasks to fulfil within the 5th commercialization stage	**Good practices**
❖ There are no mandatory tasks to fulfil during this phase within the IVDR.	❖ **Get an overview of the regulatory process from a business perspective and specifically the entrepreneur obligations. Start the company (if relevant).** Apply articles 10-16 of the IVDR, chapter 4 of RG. Start to think about and develop (or adjust) a Quality Management System for medical devices, (minimum criteria can be found in article 10(8)). Full scale QMS is not available for researchers/small companies (start-ups). Apply ISO 13485 for QMS development (when you start a company it becomes legal obligation). Consider expert involvement in case of QMS implementation. Within the QMS, well developed risk management systems is crucial, apply the necessary focus towards it. 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 overview on the regulatory requirements under IVDR can be found here: https://ec.europa.eu/docsroom/documents/33662 ❖ **Initiate the notified body selection process** It may take up to 3/4 of a year from first contact to closure of an agreement. ❖ **The development of a roadmap for IVDR implementation, includes resource requirements and a steering group. Distribution of the responsibility for the implementation of IVDR (overall/piecemeal)** ❖ **Review of supply chain regulations and role and responsibility clarifications of economic operators (authorised representatives, distributors, importers)** Remember of required registration of authorised representatives and importers according to article 28. According to article 27(2) Member States may maintain or introduce national provisions on registrations of distributors of devices which have been made available on their territory.

	In order to search for potential authorised representatives, the EAAR database can be used: http://www.eaarmed.org/ ❖ Conduct regulatory training for crew members
ACHIEVEMENTS OF THE PHASE ARE IMPORTANT FROM A REGULATORY PERSPECTIVE: COMPANY ESTABLISHMENT, DETERMINED SUPPLY CHAIN, RELEVANT QAULITY SYSTEM IMPLEMENTATION, COMPANY PREPARATION FOR THE IMPLEMENTATION OF IVDR REQUIREMENTS	

Sources: IVDR, BIC resources

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/ivd-regulatory-assistance/overview-ivd-regulation

Further reading:

- 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

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.**

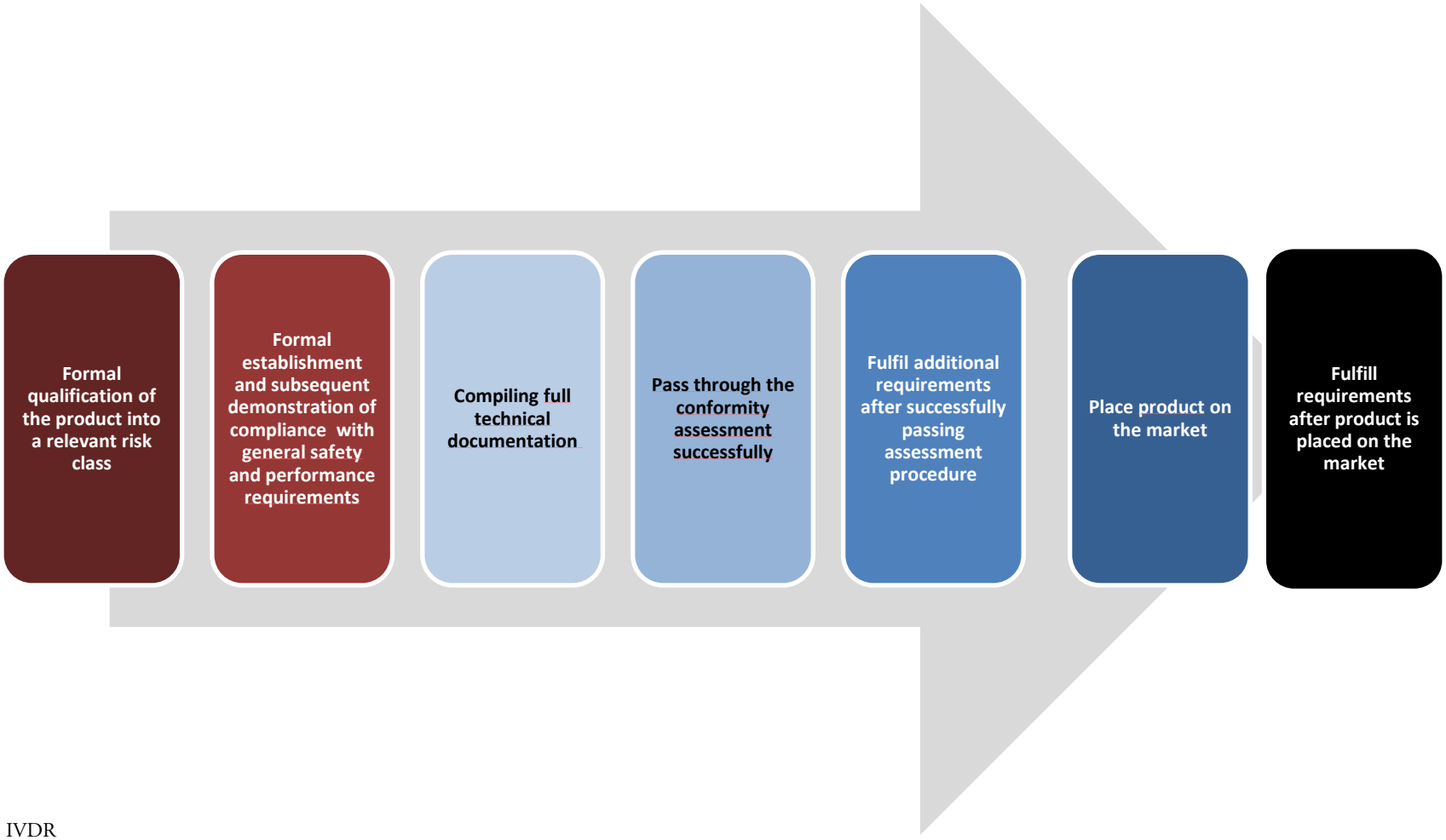
BACKGROUND:

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 costs 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 below:

Figure 15: Milestones in IVD medical device development for an enterprise from a regulatory perspective



Sources: IVDR

Figure 16: Regulatory tasks regarding industrial assay development

Regulatory tasks regarding industrial assay development

Regulatory tasks to fulfil within the 6th commercialization stage	Good practices
❖ **Address the requirement of employing a person responsible for regulatory compliance (not relevant for micro and small enterprises).** Apply article 15 of the IVDR. At the stage of drawing up the technical documentation, it is advisable that the manufacturer shall determine a PRRC that shall be responsible for activities outlined in article 15, and 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 ❖ **Determine a regulatory pathway for the product** **Apply article 48; figure 37 of RG.** The regulatory pathway depends on the risk class and intended use of the product. ❖ **Plan for developing the product technical documentation.** **Apply chapter 4.2 & 4.3 of RG.** ❖ **Requirements for providing sufficient financial coverage in respect to potential liability regarding damages caused by a defective device** **Apply Article 10(15) of the IVDR.** ❖ **Final classification of the biomarker product into an IVD risk class & verification of general safety & performance requirements** Apply article 47, annex I and annex VIII; chapter 4.1 and 4.4.1 of RG. Enterprise is responsible for the final classification of the product into a risk class: A,B,C or D and it may be conducted on the basis of product characteristics and risks related to its use. Enterprise is able to conduct classification with the assistance of scientific input. Where uncertainty exists, seek the advice of a notified body or competent national authori-	❖ Check the availability/capacity of the notified body before submitting the application ❖ Regular monitoring of the progress of prior established IVDR implementation plan ❖ Check what is the language standard for documentation in the Member State in which the notified body is established, as well as the Member States where the device is anticipated to be sold

ty. Be familiarised with IVDR requirements regarding GSPRs (annex I).

- **Verify the usefulness of data & results from research phases**

Check completeness and quality of the data. Verify that the data meets the critical criteria and determined research methods. Additionally verify what data and which results can you use for the development of the technical documentation.

- **Fulfilment of general safety & performance requirements**

Apply annex II section 4.

All GSPRs have to be covered by documentation (relevant as well as irrelevant to the product). For irrelevant requirements the entrepreneur must draw-up an appropriate explanation. Compliance with GSPRs can be assured by using harmonised standards.

IVDR harmonised standards **will be** found here: https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices_en

Currently standards under the link are harmonised under IVDD. There is no harmonized standards under IVDR yet. Monitor the standards harmonisation for IVDR and during the transition time stick to the "state of the art" approach (use relevant: ISO, GHTF/IMDRF, FDA and CLSI standards).

- **The development of technical documentation concerning product verification & validation**

Apply annex II section 6; chapter 4.2.2 of RG.

Technical documentation for product verification & validation is based on research input. It is essential to begin the product documentation from product verification & validation, because: 1) – the positive results of verification & validation are pre-requisites for registering and placing a product on the market, 2) the completion of this part of the documentation enables the completion of the other project components (details in RG). Product verification & validation requires conducted performance studies for which ethical approval and submitted application is obligatory. Apply ISO 20916 to clinical performance studies.

- **Develop full technical documentation until it is sufficient to pass the conformity assessment procedure**

Apply annex II & annex III; chapter 4.2 & 4.3 of RG.

Develop the six main parts of the documentation, according to IVDR requirements, which include, e.g. kit inserts, instruction manuals, labels, device descriptions along with its various parts. Develop the technical documentation in the most practical/ergonomic way, until it is complete and appropriate for the relevant conformity assessment procedure.	
ACHIEVEMENTS OF THE PHASE ARE IMPORTANT FROM A REGULATORY PERSPECTIVE: COMPLETE FULL TECHNICAL DOCUMENTATION, A REGULATORY PATHWAY IS DETERMINED, A PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE IS EMPLOYED	

Sources: IVDR, BIC resources

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:

Conformity assessment is a major but not merely the only obligation a manufacturer faces during the process of placing an IVD biomarker product on the market. After successful certification, the enterprise is also responsible for addressing additional requirements before the product appears on the market (e.g. CE marking) and for the fulfilment of other obligations after the product is already placed on the market (post-market surveillance requirements). **In order to place an IVD biomarker product onto the market the manufacturer must address the additional following requirements:**

Figure 17: Additional requirements to fulfil after a product has successfully passed the conformity assessment procedure

Sources: IVDR

Note:

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

After addressing the additional requirements (fig.17), the IVD biomarker product is **ready to be placed on the market.** However, this does not conclude the obligations required of the enterprise.

After product is placed on the market, another requirements are expected to be fulfilled. At this stage 3 main groups of obligations appears:

- Post-market surveillance (art. 78-81)
- Vigilance (art. 82-87)
- Market surveillance (art 88-95)

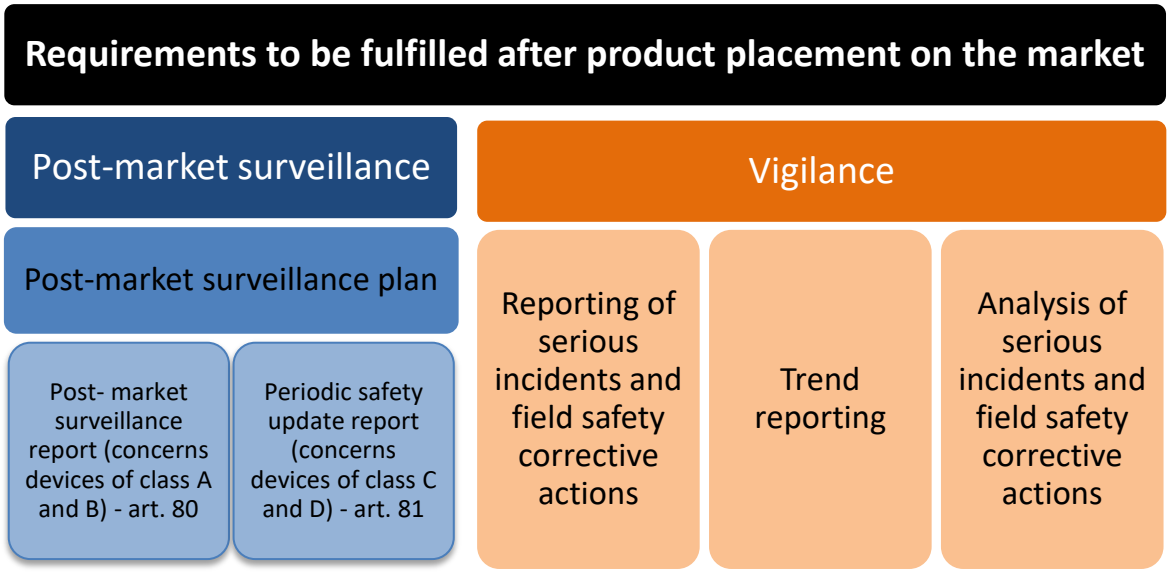
(direct - activities carried out by the entrepreneur, and indirect - activities carried out by the competent authorities, but concern the entrepreneur)

The document is focused on the direct obligations allocated to entrepreneur. The producer is also obliged to cooperate with the competent authorities regarding market surveillance.

Direct Obligations

Requirements regarding **safety** assurance based on the **post-market surveillance system** is an integral part of the quality management system of the enterprise. The surveillance system facilitates the collection of data by the producer, which is subsequently submitted by the company (or manufacturer) to **the electronic system on vigilance and post-market surveillance** (an element of the Eudamed database). This data allows for documentation updating, identifying the need for action, detecting and reporting trends, etc. (article 78). The manufacturer cooperates with the entities responsible for ensuring the safety of *in vitro* diagnostic devices.

Figure 18: Requirements (direct) to be fulfilled by the enterprise after a product is placed on the market



Sources: IVDR

Notes:

- **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.

All these requirements are fulfilled through an electronic system, which is also used by the relevant authorities of the Member States, the Commission and the notified bodies in the relevant areas. The manufacturer is obliged to cooperate with them in regards to market surveillance (chapter VII, section 3).

Indirect Obligations

Market surveillance activities overview

Competent authorities carry out market surveillance activities on the basis of annual surveillance activity plans, which they draw up, taking into account European market surveillance programs (developed by the MDCG) and local circumstances.

Evaluation of devices suspected of presenting an unacceptable risk or other non-compliance:

If, based on the data obtained or other information, the competent authorities of a Member State have reason to suspect that the device:

a) *may present an unacceptable risk to the health or safety of patients, users or other persons, or to other aspects of the protection of public health; or*

b) *otherwise does not comply with the requirements laid down in the Regulation*

competent authorities conduct an assessment of this product covering all the requirements set out in the IVDR regarding the risks generated by the product or other non-compliance of the product. If competent authority finds that the product presents an unacceptable risk to the health or safety of patients (a), in this case the procedure described in art. 90 & 91 is relevant. If they find that the product does not comply otherwise with the requirements (b), then the procedure described in art. 92 is relevant.

When relevant, economic operators cooperate with the relevant authorities.

The Member State may introduce preventive protection measures to a product with a potential risk (article 93).

Figure 19: Regulatory tasks regarding commercial launch and clinical implementation stage

Regulatory tasks regarding commercial launch and clinical implementation stage

Regulatory tasks to fulfil within the 7th commercialization stage	Good practices
❖ **The passing of the conformity assessment procedure successfully** Conformity assessment procedures differ in complexity and scope. Follow previously determined regulatory pathways relevant to product risk class. Cooperate with the notified body in order to pass the procedure. Link to the NANDO database: http://ec.europa.eu/growth/tools-databases/nando/ ❖ **Address the additional requirements before the product is placed on the market: affix CE mark, prepare an EU declaration of conformity, submit product notification to the competent authority, prepare the certificate of free sale** Affix CE mark according to article 18 and annex V. Prepare UE declaration of conformity according to article 17 and annex IV. Prepare notification to the competent authority (template on the website of the competent authority) and submit the relevant documentation. Prepare the certificate of free sale according to article 55 (template on the website of the competent authority). ❖ **Complete the IVD medical device registration** Apply article 26 & article 28; chapter 4.2.1 of RG. Proceed through the registration procedure within the EUDAMED database.	❖ Check for the use of valid templates, e.g. conformity assessment, competent authority notification, etc. (available at relevant websites). List of the authorities can be found in NANDO database as well. ❖ The declaration of conformity shall contain all the information required for identification of the Union legislation to which the declaration relates, therefore, if there are some aspects not covered by the IVDR, the manufacturer can still drawn up an individual declaration (details in the description) ❖ Monitoring the expiration dates of conformity certificates ❖ Active monitoring of the regulatory environment in the case of amendments Track the European Commission website: https://ec.europa.eu/growth/sectors/medical-devices_en and potential amendments on the IVDR: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0746

PLACING PRODUCT ON THE MARKET

- **Fulfil obligations regarding the post market surveillance system and vigilance requirements - continuous process through the entire product lifecycle**

Apply articles 80-84; chapter 3.7 and 4.3 of RG.

Fulfil the following obligations when a product is already on the market: a) Report any serious incidents and any field safety corrective actions (in accordance with art. 82 paragraph 1 and art. 84 paragraph 5), and also in the form of periodic summary reports (art. 82 paragraph 9) b) Trend reporting (in accordance with art. 83) c) Reporting on safety (art. 80 and 81), d) Analysis of serious incidents and field safety corrective actions, among others, prepare safety notices (in accordance with art. 84 paragraph 8).

- **Cooperation with national entities in order to ensure safety (market surveillance requirements) – a continuous process of supervision by the competent authorities**

Requirements indirectly concern the enterprise after a product is placed on the market. If necessary, and/or any non-compliance occurs, be prepared: - 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 - to take all appropriate and duly justified corrective action to bring the device into compliance with the requirements of IVDR - to restrict the availability of the device on the market - to subject the availability of the device to specific requirements - 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.

ACHIEVEMENTS OF THE PHASE IMPORTANT FROM A REGULATORY PERSPECTIVE: CERTIFICATES OF CONFORMITY ASSESSMENT ARE OBTAINED, CE MARK IS AFFIXED, CERTIFICATE OF FREE SALE IS PREPARED, EU DECLARATION OF CONFORMITY IS PREPARED, PRODUCT NOTIFICATION TO AUTHORITY IS SUBMITTED, PRODUCT IS PLACED ON THE MARKET, CONTINUOUS FULFILLMENT OF POST-MARKET OBLIGATIONS

Sources: IVDR, BIC resources

4.IVDR overview

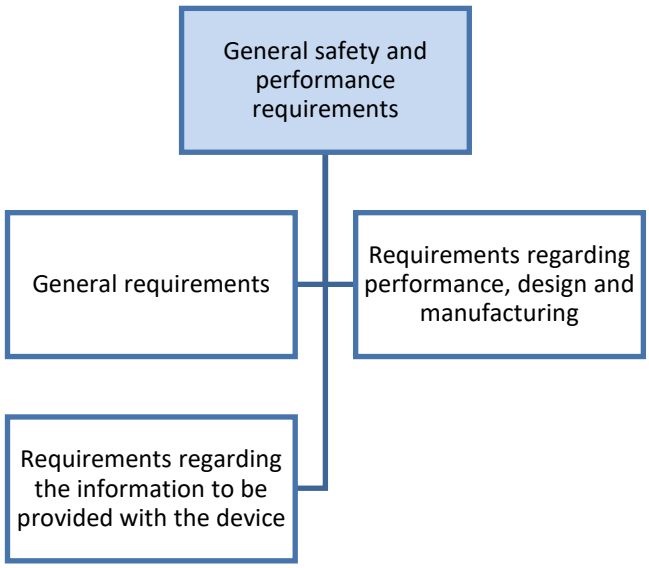
4.1. General safety and performance requirements

Compliance with the relevant general safety and performance requirements are obligatory for IVD medical devices, and technical documentation must be developed in compliance with the same requirements. GSPRs are determined according to product design, characteristics and performance of the device and risks related to its use. Checklist-based GSPRs, pointed out in annex I, should be treated as a framework for compiling the technical documentation. The decision of which GSPRs are relevant/irrelevant to the product is in accordance with the manufacturer. General safety requirements inform which requirements are relevant for a suitable product and which need to be fulfilled in order to introduce the product to the market. The manufacturer is also obliged to provide an explanation as to why, according to them, certain GSPRs are not relevant and do not apply.

General safety and performance requirements are divided into 3 main groups (fig.20), and can be met by the appropriate method / methods used to demonstrate compliance, and thus by applying:

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

Figure 20: General safety and performance requirements structure



Sources: IVDR

In addition, the entire technical documentation has to be developed in accordance with the GSPR, the information related to the justification of compliance with a specific general safety & performance requirement is placed in a separate part of the documentation called 'general safety and performance requirements' (in accordance with figure 21).

Initial assignment of relevant general safety and performance requirements to appropriate types of IVD medical devices would significantly improve the process of compiling technical documentation for manufacturers, who do not have such experience or introducing an IVD belonging to a different risk class than they have introduced in the past.

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 21: Relation between QMS, general safety and performance requirements and technical documentation

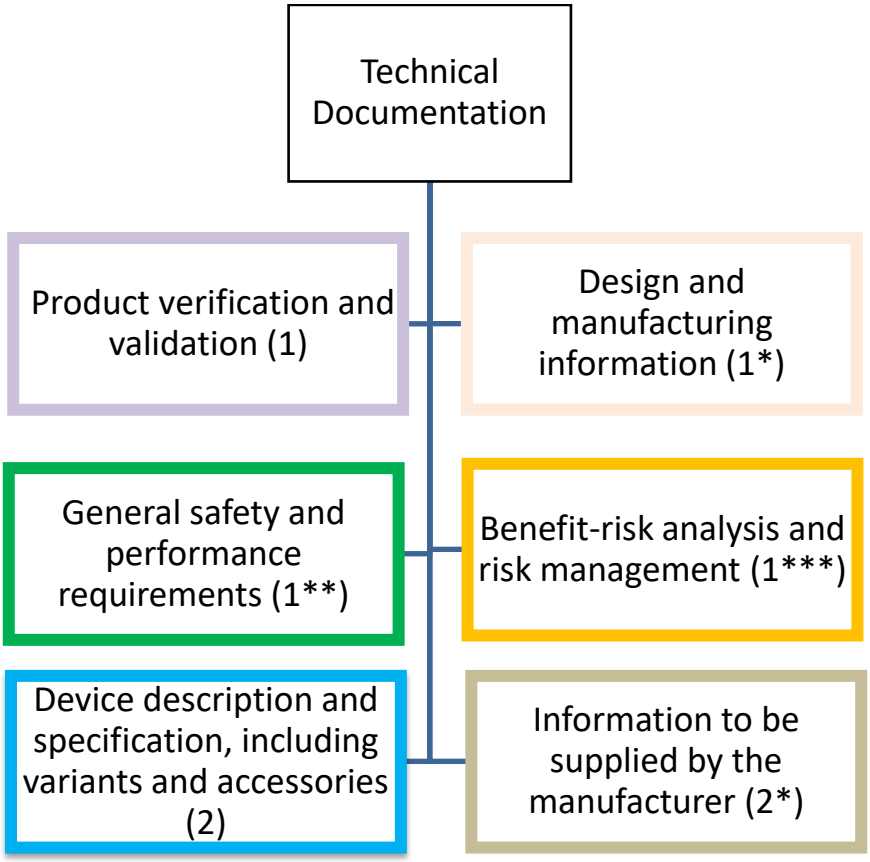
Sources: IVDR

4.2. Technical documentation

The technical documentation of a device (annex II) 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. Colour coding, as well as the order of completion of the relevant parts of the technical documentation (in the brackets) are applied.

Figure 22: Technical documentation of an IVD product - structure



Sources: IVDR

Key:

Based on the IVDR, collecting individual parts of Technical Documentation requires*:

Conducting a performance study and its evaluation (chapter 4.2.2 of RG).
Gathering this part of the documentation does not require additional activities (manufacturer description – no further actions is needed).
Confirmation of conformity to relevant general safety and performance requirements (chapter 4.1 of RG).

Implementation of the risk management system (annex I, chapter 1), 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.

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.

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.

*Requires means that without carrying out crucial processes shown in the color-coded list below, it will be impossible to complete a given part of the technical documentation. Manufacturers have to **remember that the fulfillment of merely certain requirements (and the gained documentation related to these fulfilled requirements), does not ensure the completeness of the relevant portion of the technical documentation, however those processes are essential to complete it.** Full description of the technical documentation can be found in the IVDR(annex II).

Crucial processes, in respect to the color-coded list above, e.g. manufacturer and device registration and performance studies and their evaluation, are characterized in subsequent sub-chapters (from 4.2.1 and 4.2.2)

The proposed order to begin developing a particular portion of the technical documentation (in the brackets of figure 21):

1*,1**,1*** - these individual portions of the documentation process may be initiated simultaneously for the "product validation & verification", however, some dependents exist: risk management (1***) cannot be completed before performance studies are conducted, 1** cannot be completed before performance studies are conducted. Device description (2) cannot be completed without the manufacturer & device registration (and registration cannot be conducted completely without the submission of the "safety & performance summary", which requires conducted performance studies). Information supplied by the manufacturer (2*) cannot be completed without an UDI carrier, which requires product registration.

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

Notes:

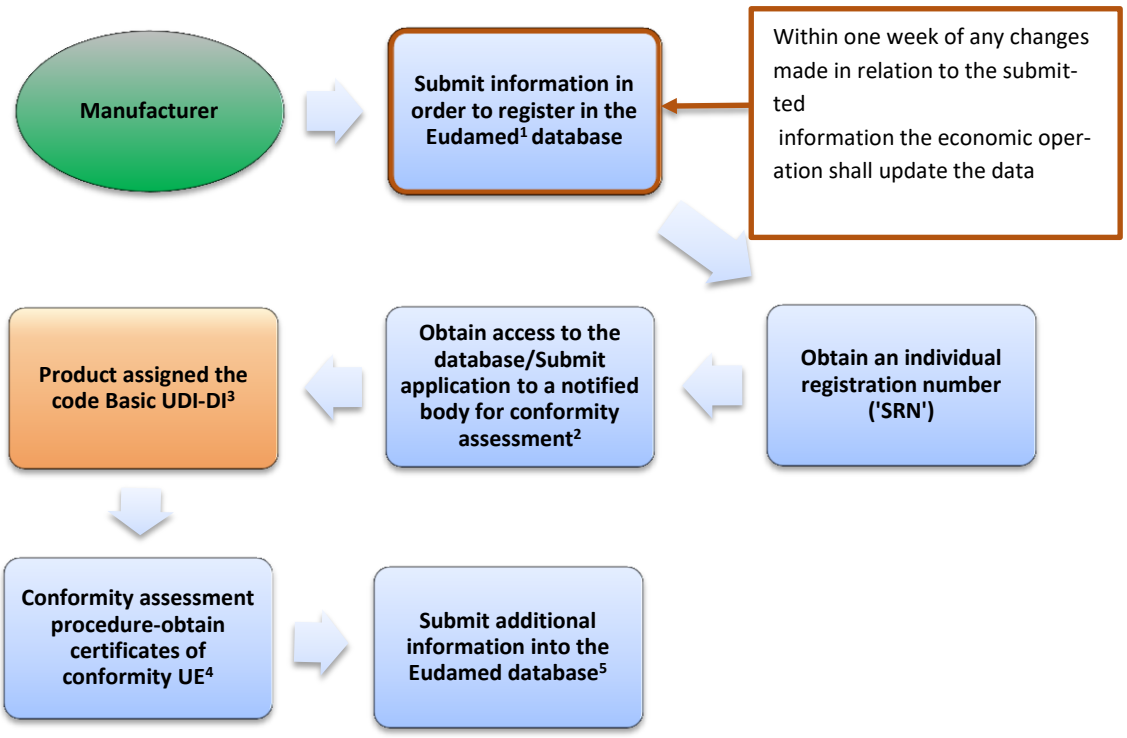
- The Post-market surveillance report/Periodic safety update report is due first time one year after 26 May 2022 for IVD medical devices certified under IVDR.
- Post market surveillance report applies to devices of classes A and B, and Periodic safety update report applies to devices of classes C and D.
- Voluminosity and complexity of technical documentation and technical documentation on post-market surveillance are specific, and depend on concrete IVD medical device characteristics.
- Technical documentation has to be prepared simultaneously with the technical documentation on post surveillance (except for reports concerning the obligations which ensue after a product is placed on the market).

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 key description below).

Figure 23: 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.

Notes:

- 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

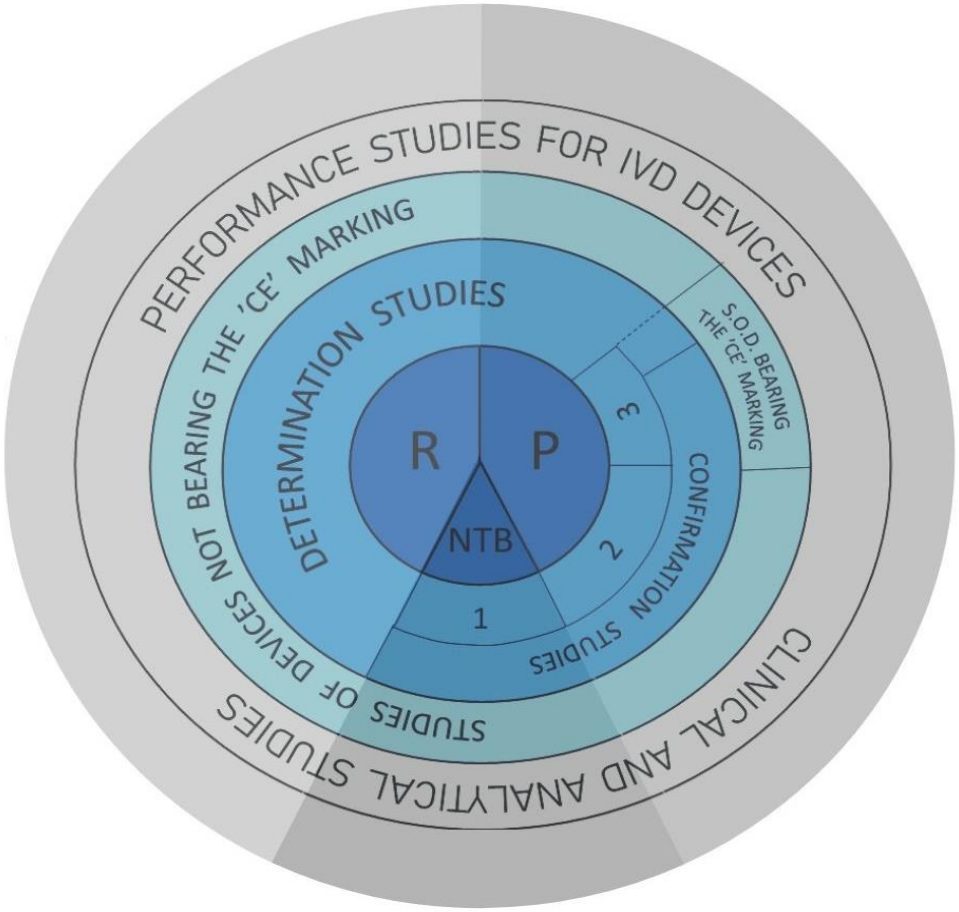
3. to monitor/update performance evaluation throughout the life cycle of a device ("PMPF studies").

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 24: Types of performance studies and responsibilities of each study



Sources: IVDR, BIC resources

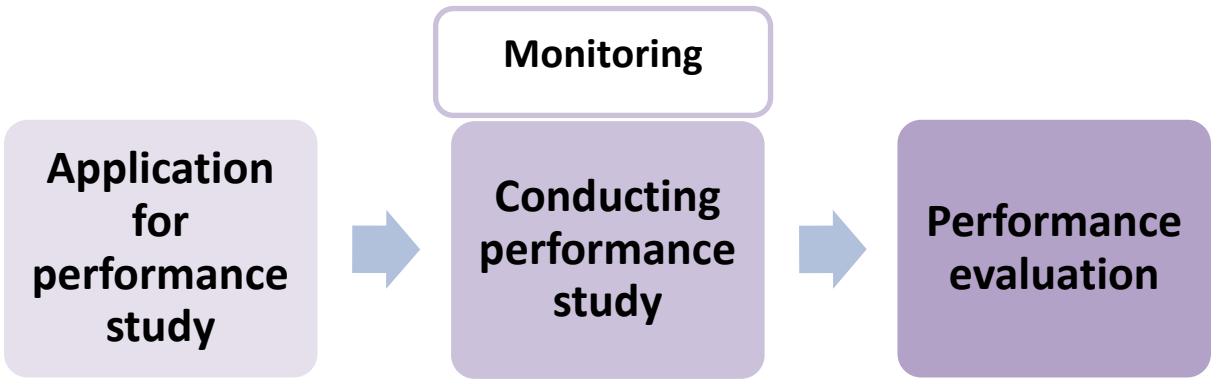
Key:

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

The figure above shows the scope of studies divided between the 3 main participants: researcher, notified body and producer. It also introduces different types of the performance studies applied to products being placed/already placed on the market.

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

Figure 25: Performance study process-general scheme



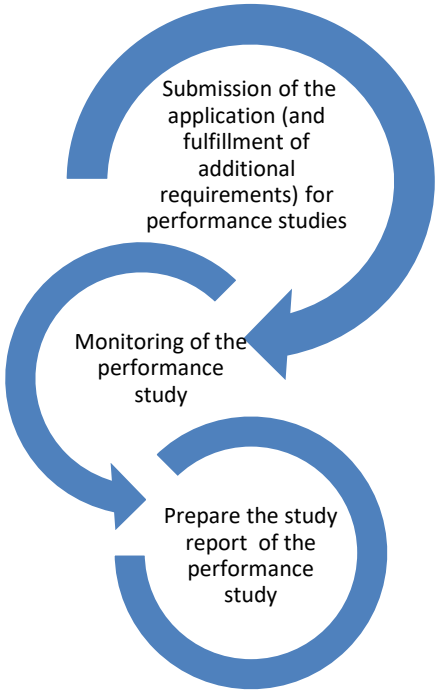
Note:

- Completed performance evaluation enables completion of technical documentation regarding product verification & validation (and other parts of the documentation, in accordance to figure 22)
- 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 26: General role of the sponsor in the performance study process



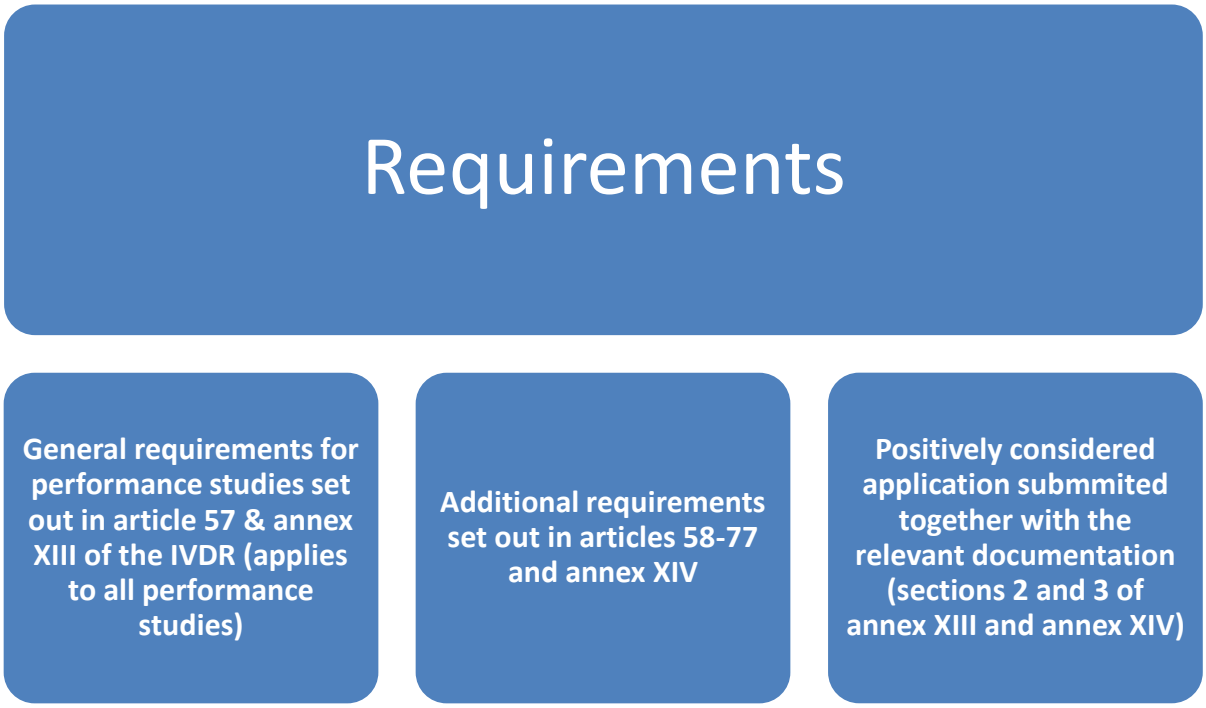
Sources: IVDR

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) and additional (article 58, annex IV) 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 27: Requirements needed to be fulfilled before a performance study is initiated



Sources: IVDR

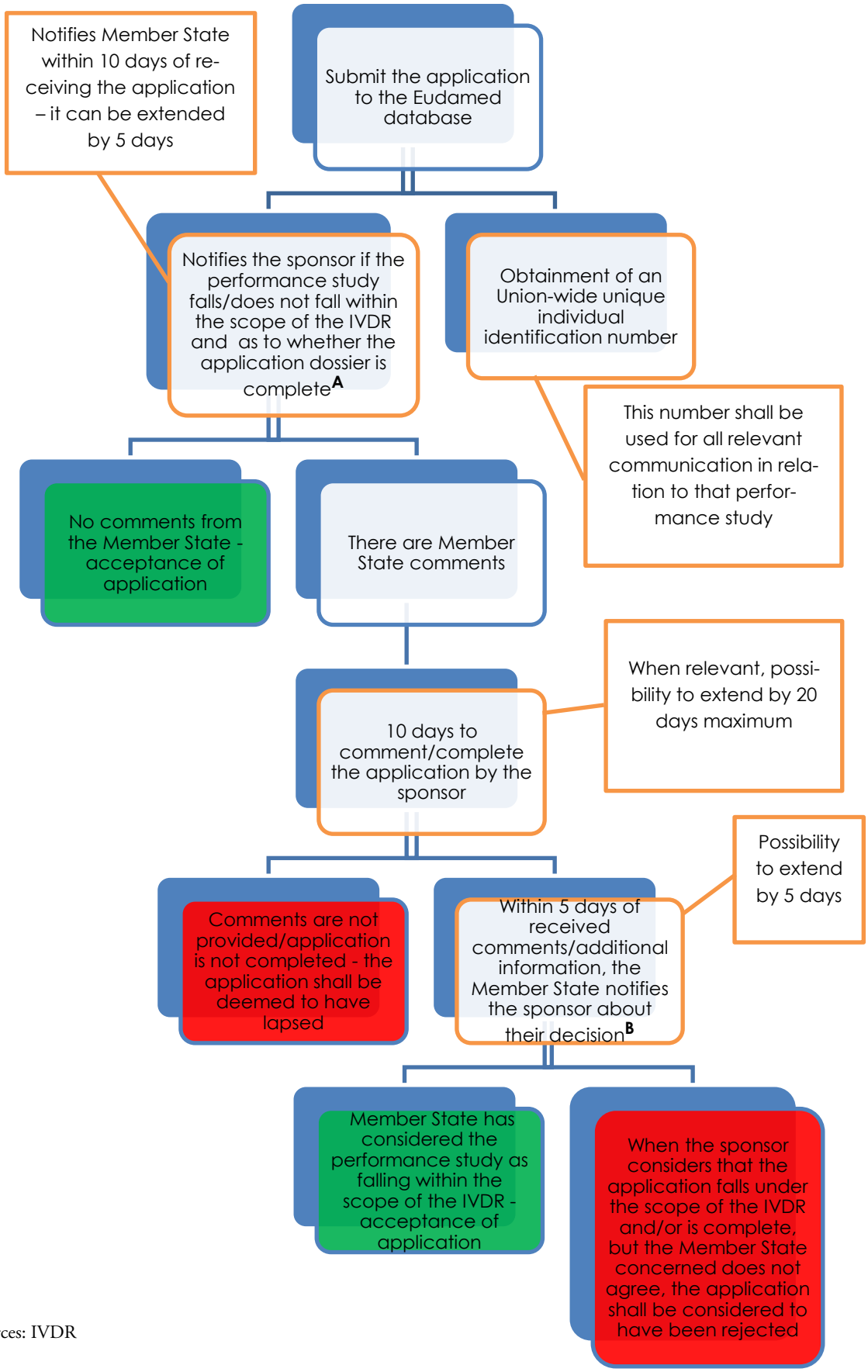
Application:

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) accompanied by the documentation referred to in sections 2 and 3 of annex XIII and in annex XIV.

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.

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

Figure 28: Sponsor's 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).

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

After the positively considered application and fulfilled additional requirements (relevant to a specific IVD biomarker product), the sponsor proceeds to execute the performance study.

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):

***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.*

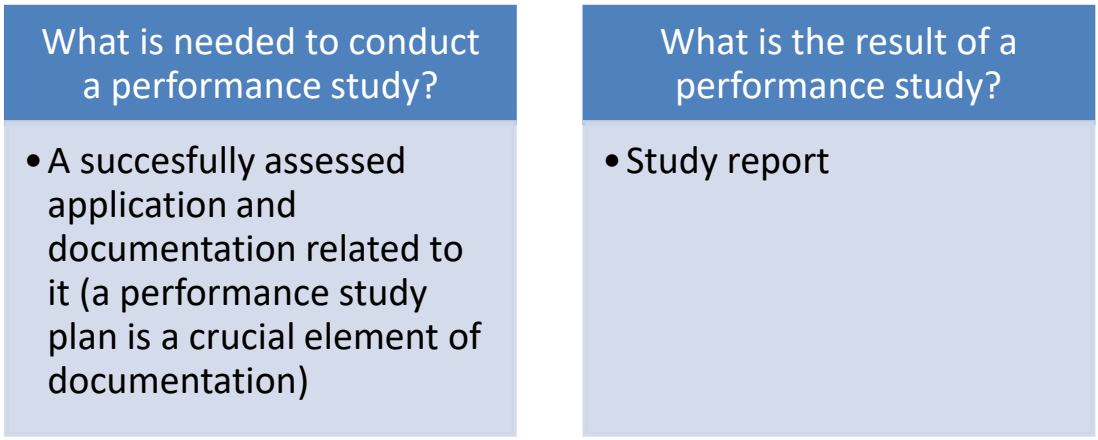
Clinical performance studies shall be performed unless due justification is provided for relying on other sources of clinical performance data.

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 29: Documentation related to performance study



Relation between performance studies and quality standards:

Analytical performance studies, as well as clinical performance studies, 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, IMDRF standards or Good Clinical Practice (GCP) for clinical performance. GCP consists of 4 phases of study, preceded by a preclinical stage, during which the concept of a new therapeutic method is verified on cell and animal models.

4.2.2.3. Monitoring of performance studies

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

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) he/she notifies the Member State, via the

electronic system, within **one week*** informing of the reasons and nature of these changes - updates the documentation referred to in annex XIV, 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)).

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, the Member State **30 days** before the performance study is to be conducted, if:

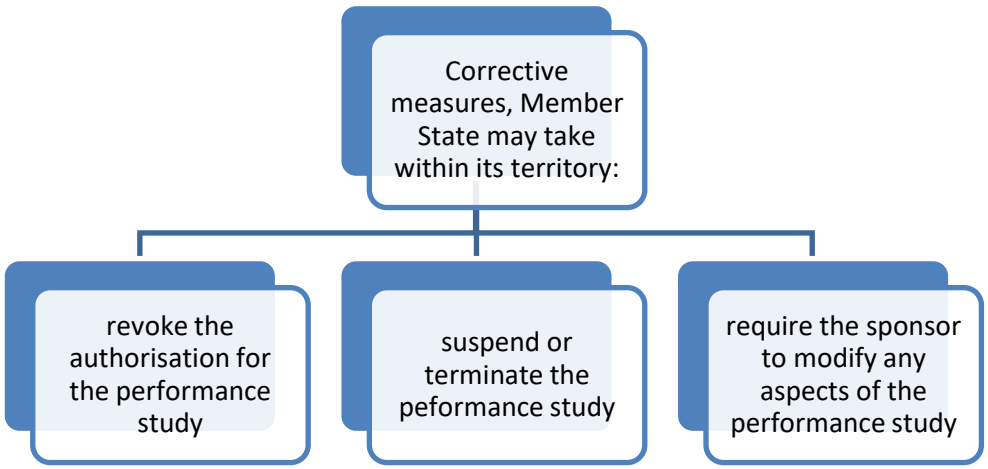
a) the performance study is to be conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking - 'PMPF study' (in accordance with article 70), and
b) the performance study would involve submitting subjects to additional procedures to those performed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

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 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), 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):

Figure 30: Corrective measures-structure



Sources: IVDR

*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.

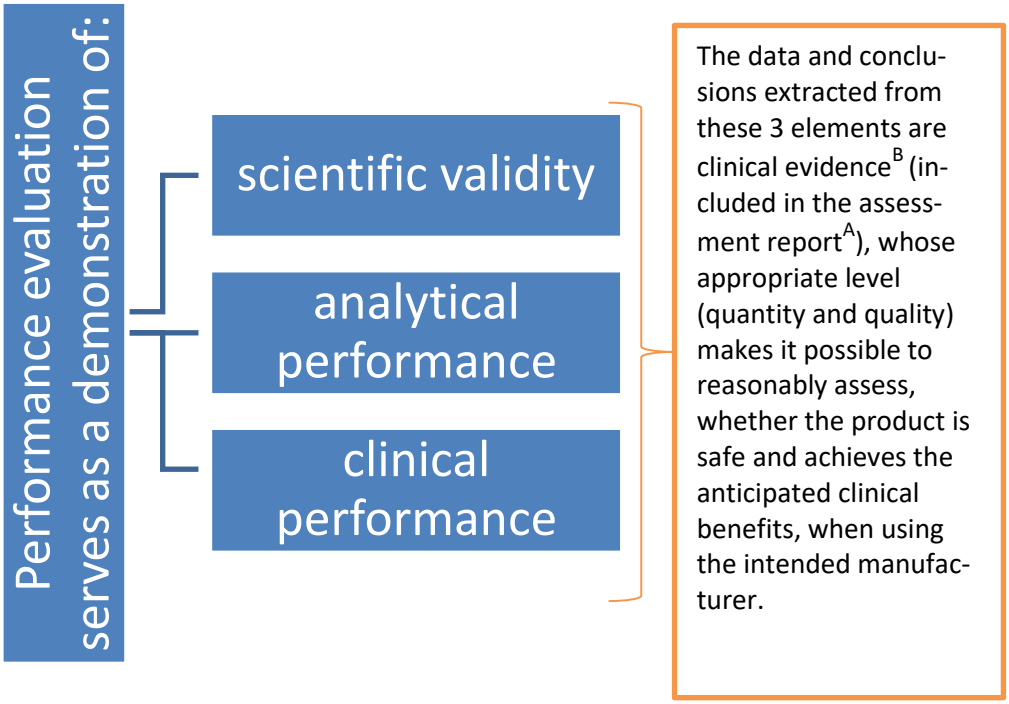
4.2.2.4. Performance evaluation

The performance evaluation is conducted after the performance study in an accurate and objective manner, taking into account both, **beneficial and unfavorable data**. Performance evaluation, next to analytical performance and clinical performance (justified by relevant performance studies), encompass also scientific validity.

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 31: 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?

According to IVDR:

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 analytical performance

The manufacturer shall demonstrate the analytical performance of the device in relation to all the parameters described in chapter 5.2.2.2 of Regulatory Guide.

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 the performance characteristics described in chapter 5.2.2.2 of Regulatory Guide. chapter II.

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).

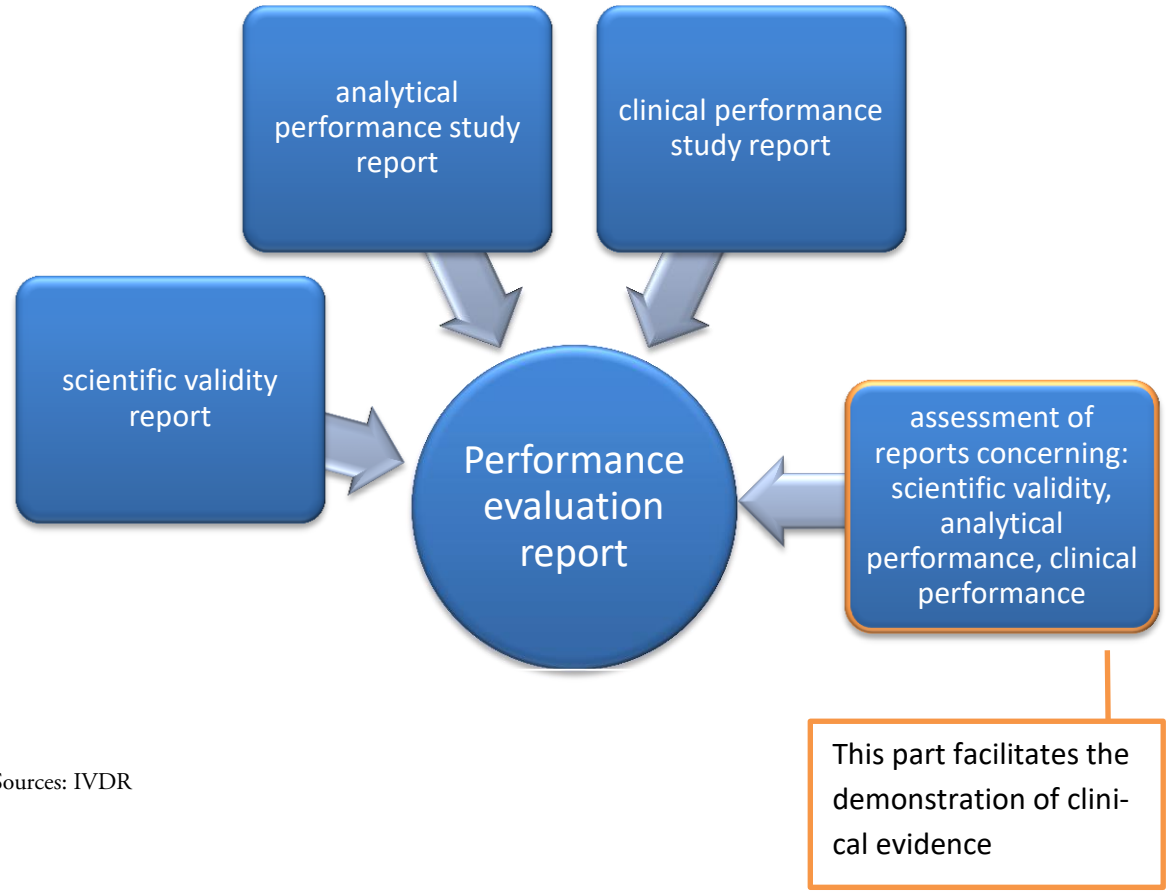
Documentation:

Figure 32: 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 33) - 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:

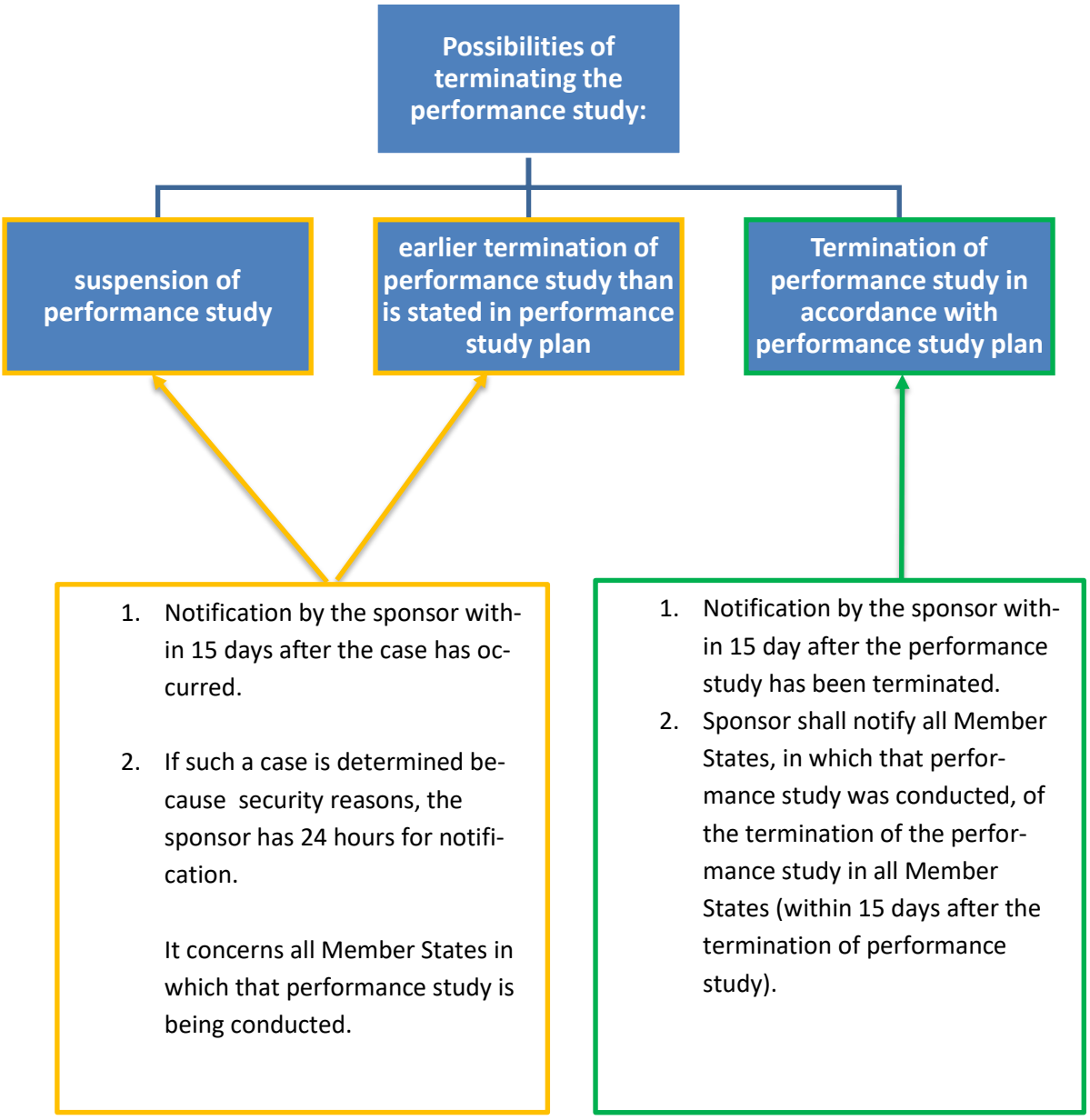
Figure 33: Structure of performance evaluation report:



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.34) 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 34: 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).

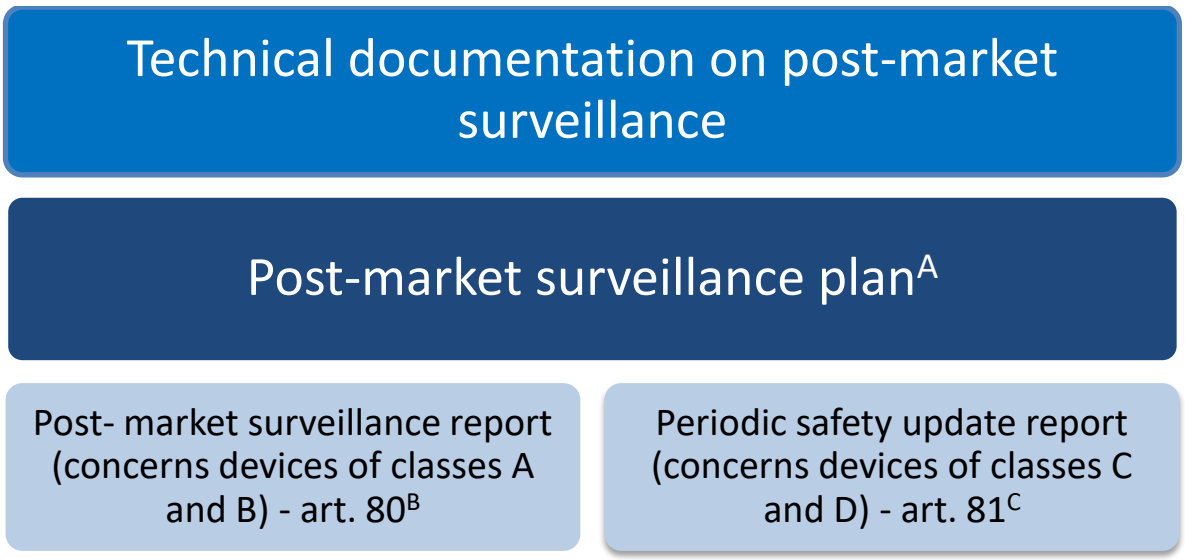
The report shall become publicly accessible in the electronic system (EUDAMED), no later than at the time of registration of the device, in accordance with article 26, and before it is placed on the market.

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).

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 35: 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 pre-

ventive 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

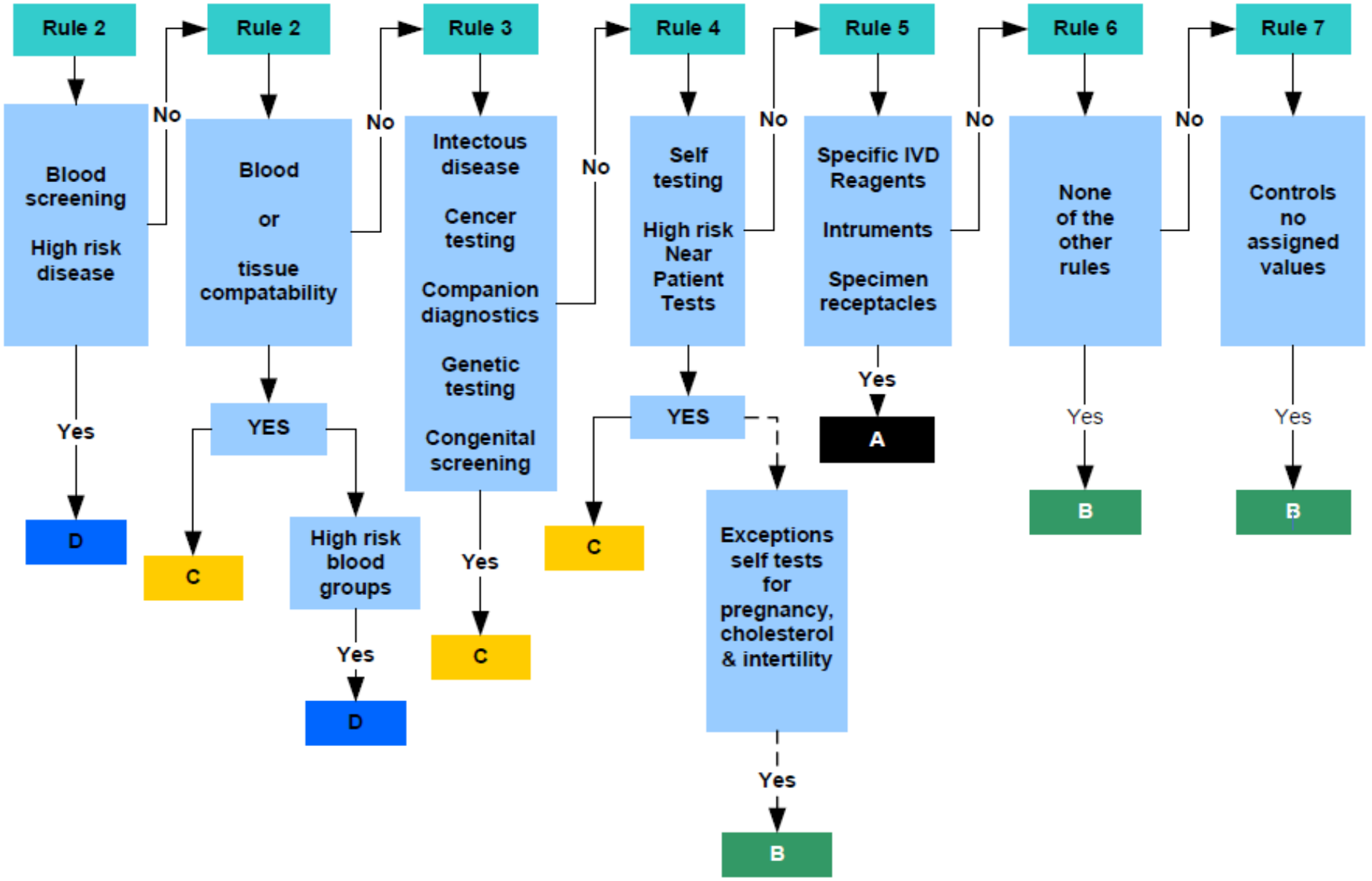
Each course of the conformity assessment procedure of a medical device for in vitro diagnostics depends on the classification of the product in a given risk group (A, B, C, D) and in a given generic device group. For this reason, in this chapter, the group classification of medical devices for in vitro 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 *("*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. 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:

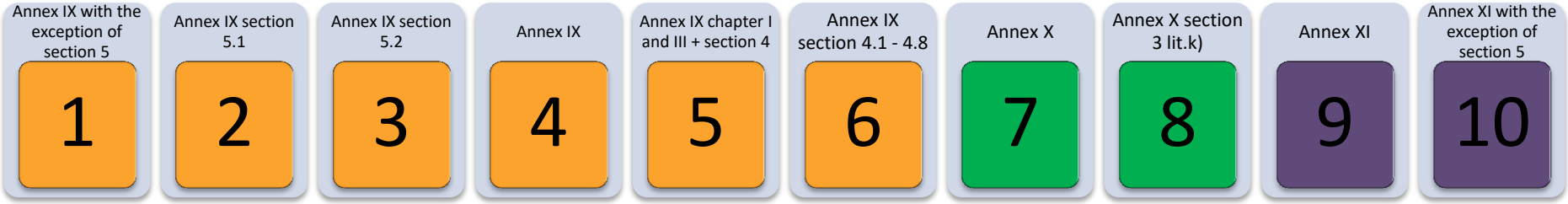
Figure 36: IVD medical classification according to annex VIII - IVDR rules



4.4.2. Course of conformity assessment procedure for every group and category of products

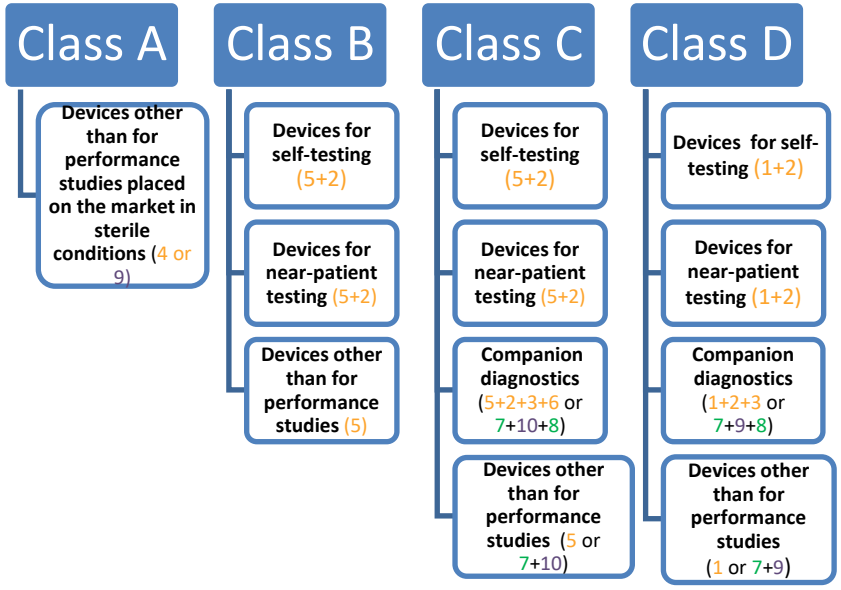
Figure 37: Course of conformity assessment procedure for every group and category of products

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:

Some of the product categories/types shall be covered by two conformity assessment procedures (interchangeably). In this case, the procedures are separated by the word "or" in the table.

Each full conformity assessment procedure consists of relevant elements. Elements of procedures have been coded in two ways: numerically and by colour. Numbers have been assigned as in the above diagram, and the meaning of the colours is introduced below:

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 orange (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 - green colour (annex X of the Regulation) and conformity assessment based on production quality assurance in purple (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.

Only A-class devices, due to the low risk related to their use (exemption for devices placed on the market in sterile conditions) - the manufacturer can conduct a self-assessment procedure, details can be found in chapter 4.4.3. of Regulatory Guide

4.4.3. Class A-additional information

Devices of A class, other than for performance studies and product placement on the market in non-sterile conditions, do not require the participation of a notified body in the conformity assessment procedure. **A self-assessment procedure is applied to these type of products.**

After completing the full technical documentation (annexes II and III), and submitting a statement of conformity of the products, by issuing an EU Declaration of Conformity (according to article 17 and annex IV), **devices of A class do not require a conformity assessment procedure with the participation of a notified body due to the low risk associated with the use of these devices**. However, if the devices of A class are going to be placed on the market in sterile conditions, the manufacturer applies the procedures set out in annex IX or annex XI. The scope of participation of the notified body in this case is limited to aspects related to obtaining, ensuring and maintaining sterile conditions.

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 37 of RG).

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).

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) 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). 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.

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

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).

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.**

Further reading on U.S system:

- 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:

1. https://www.fda.gov/medical-devices/products-and-medical-procedures/vitro-diagnostics
2. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia
3. https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products

5.Summary

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.

6.FAQ (Frequently Asked Questions)

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 & 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

7.References

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