Interreg Baltic Sea Region

EUROPEAN UNION

EUROPEAN REGIONAL DEVELOPMENT FUND

BIOMARKER COMMERCIALIZATION

The Biomarker Commercialization (BIC) Guide

For in vitro diagnostics

Lead author: **Valerie Daussin**

Contributing authors: **Piia von Lode, Paweł Myszczyński, Konstantin Denessiouk, Merja Tieaho, Teppo Laaksonen**

AALBORG UNIVERSITY HOSPITAL

WPT WROCLAW TECHNOLOGY PARK

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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LIST OF ABBREVIATIONS AND ACRONYMS

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AUC: Area Under the Curve

BUDI: Basic Unique Device Identification

CDA: Confidential Disclosure Agreement

CE: Conformité Européene

CEO: Chief Executive Officer

CLIA: Clinical Laboratory Improvement Ammendments

CLSI: Clinical and Laboratory Standards Institute

CMS: Centers for Medicare & Medicaid Services

CV: Coefficient of Variation

DNA: Deoxyribonucleic Acid

EU: European Union

EUDAMED: European Database on Medical Devices

FAIR: Findable, Accessible, Interoperable and Reusable

FDA: Food and Drug Administration

FTO: Freedom-To-Operate

GDPR: General Data Protection Regulation

GHTF: Global Harmonization Task Force

GLP: Good Laboratory Practices

GSPR: General Safety and Performance Requirements

HTA: Health Technology Assessment

ID: Identification

IFU: Instructions For Use

IMDRF: International Medical Device Regulators Forum

IP: Intellectual Property

IPR: Intellectual Property Rights

ISO: International Organization for Standardization

IVD: In Vitro Diagnostic

IVDR: In Vitro Diagnostic Regulation

LOB: Limit of Blank

LOD: Limit of Detection

LOI: Letters of Intent

LOQ: Limit of Quantification

mRNA: messenger Ribonucleic Acid

NDA: Non-Disclosure Agreement

NPV: Negative Predictive Value

PE: Performance Evaluation

PMS: Post-Market Surveillance

POC: Point-of-Care test

PPV: Positive Predictive Value

PRRC: Person Responsible for Regulatory Compliance

QC: Quality Control

QMS: Quality Management System

QPBR: Quality Practices in Basic biomedical Research

R&D: Research and Development

RNA: Ribonucleic Acid

ROC: Receiver Operating Characteristics

RT: Room Temperature

RUO: Research Use Only

SD: Standard Deviation

SHA: Shareholders Agreement

SME: Small and Medium Enterprises

SRS: System Requirement Specification

TTO: Technology Transfer Office

UDI: Unique Device Identification

URS: User Requirement Specification

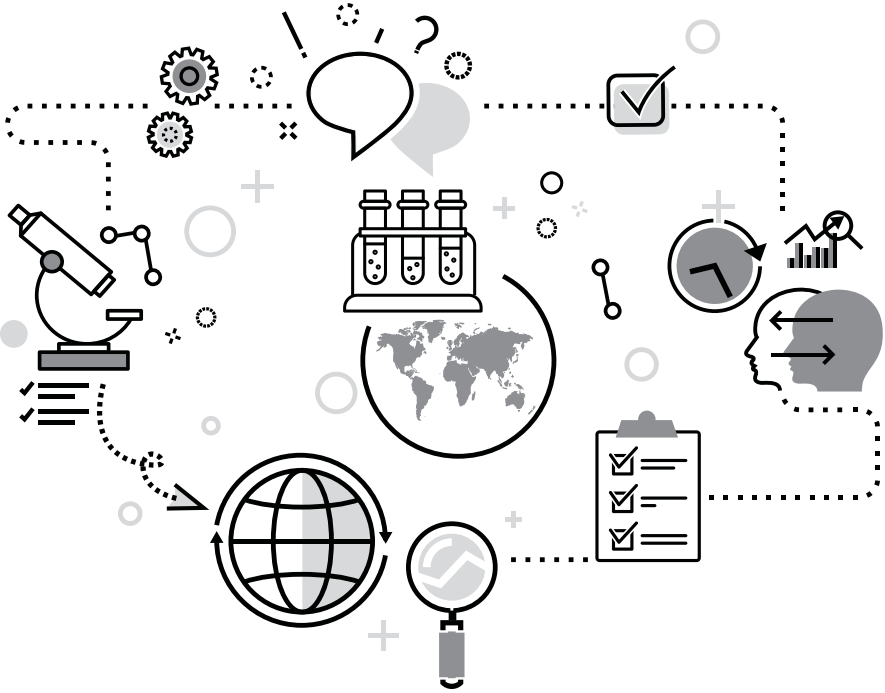
VC: Venture Capital

VOC: Voice Of Customer

WBS: Work Breakdown Structure

WP: Work Package

PREFACE



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Although half of all clinical decisions are based on In-Vitro Diagnostics (IVDs), introduction of new IVD products into clinical practice still poses a significant challenge. Every year a great number of new biomarkers are identified and linked scientifically and clinically to diagnosis, prognosis and prediction of diseases and their treatments, but only 2% of those markers will ever convert into clinical tools.

Bringing an IVD into the market is complicated, requiring time and resources as well as a structured process to obtain regulatory approvals at a later stage. Research institutions across Europe and other countries generally place their resources for research-driven innovation within their Technology Transfer offices, but dealing with biomarker inventions based on biological markers requires a specific understanding of the field which is not always accessible. The development of biomarker diagnostic tools requires multidisciplinary competences (medical, biochemical, engineering) and a proper coordination of those skills. The roles and attribution of tasks for each stakeholder are important for efficiency.

The Biomarker Commercialization (BIC) Consortium, a partnership across the Baltic Sea Region and beyond (financed by the Interreg Baltic Sea Program), aspired to contribute to improving the development of biomarker-based diagnostics. By putting their knowledge and network together, with the support of a very dedicated advisory board, the BIC Consortium managed to create and develop a set of meaningful tools for supporting the development and translation of biomarker inventions into clinical products. These tools provide step-by-step guidance, explanation and inspiration to research groups and SMEs interested in launching IVDs onto the market.

The journey has been long and tedious. For 4 years, we have compiled knowledge, collected information and feedback, tested the developed tools with volunteers, researchers and SMEs located in the Baltic Sea region, developed a communication and promotion strategy, and expanded the network of people interested in the development of IVDs across Europe. This work has culminated in a final set of tools

that cover the lifespan of a biomarker invention from discovery through to market launch. While this book specifically compiles the BIC guide for development and commercialisation of biomarkers, The Biomarker Commercialisation website (www.biomarker.nu) developed by the consortium comprises many other essential resources, such as guidelines for regulatory approvals of IVDs, an educational toolbox with many useful tools for either teachers or biomarker developers, and guidelines for TTOs regarding their selection and understanding of biomarker inventions.

The complete material is freely available on the website, and we hope that the work done will help many people around us to tackle the development of IVD products with a better understanding of what lies ahead.

This work would never have been possible without the immense commitment, enthusiasm, and solidarity of the BIC Consortium partners, the advisory board, the secretariat of the Baltic Sea Region Interreg Program and the many researchers, people from industry, investors and all other participants in this great collaboration.

Thanks to all and enjoy,

Valerie Daussin

Senior Business Developer,
Aalborg University Hospital,
Project Leader BIC consortium

INTRODUCTION

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The Biomarker Commercialization Consortium has created a series of books containing relevant and useful material that will support, guide and give structure to the complex and regulated process of bringing a biomarker-based *in vitro* diagnostic successfully to the market.

This book translates the content of the BIC Guide tool from the BIC Commercialization website (www.biomarker.nu) into textbook format. Therefore, some of the original interactive features of the website were adapted in order to translate the full content of the material found on the website. All the links to external material are presented in the form of a QR code, that can be accessed by scanning it with a scan reader, which is available in most portable devices. Moreover, we also wanted to follow the organizational structure of the commercialization process described on the website, thus, in this book, the chapters are presented in a way that resemble the continuity of the different phases of the commercialization process on the website.

The commercialization process is divided into three main stages called **Research, Transfer and Market**. Each stage represents a level progress of the translation of the biomarker invention into robust IVD test. The aim of the Research stage is to transform your biomarker invention into a prototype assay. You might be ready to go to the next stage, called Transfer, once you have progressed into a beta prototype and demonstrated the technology supporting the determination of your biomarker invention. The final stage is Market. This is when your IVD test linked to your biomarker invention is ready to be placed onto market after complying with all regulatory approvals.

In this book, each chapter represent the different **Phases** of the commercialization process. The Research stage has four phases, the Transfer stage has only one phase, and the Market stage has two phases. Phases have specific outcomes based on an array of actions and activities aiming at the scientific, commercial and regulatory evaluations. Phases follow a systematic order both on the website and in this book, ensuring that they will be approached in a stepwise manner, although it

is obviously possible to go back to previous phases as necessary in order to secure the success of each activity.

Each phase has a short running-title, a number and a **technology readiness level (TRL)** associated thereof. TRLs are another way to track the development of your biomarker-based IVD, aiming a specific goal. Typically, you will find one TRL aligned with each phase, but in the Maturation phase and in the Launch phase you will find two TRLs assigned.

Each chapter begins with a list of **Phase Description**, which is a concrete list, that will prepare you for the upcoming actions. This list of activities can comprise both the scientific-technical aspects, and the commercial or regulatory aspects. The chapter also contains a list of **Phase Achievements**, which is a summary of outcomes expected for a given phase. You can consider this list as a summary of milestones of your commercialization journey.

The core content of each chapter is the list of **tasks**. Each task has a number and a title, that denotes the required outcomes. The numbers are there just to give a sense of order or for follow- up purposes, and in no way are they indicating the relative importance of each task. Firstly, you will see the list of tasks from the **scientific and technical evaluation**, followed by the **commercial evaluation** and finally the **regulatory evaluation**. An infographic as header will guide you into the different evaluation tracks within each phase.

The tasks are intended to be as comprehensive as possible. Some tasks are denoted as questions, and some are plain statements, some might be very specific and others broader, but feel confident that they are all relevant for the process. Amongst some of the tasks you might find a diagram indicating a **related task.** Follow the stage, phase and task number to get orientation. The related tasks are intended to raise awareness that some tasks can be interconnected in order to be fully completed.

A QR code is provided to access the content of task related (external) links and available material associated to some tasks. **Task related (external) links** are a source of supplementary information or external material that will provide further information regarding a given level of readiness of your biomarker invention. Documents like Medical Device Regulatory Guides or Business Model Canvas are provided. **Available material**, on the other hand, leads the reader to documents containing best practices or tips related to a given task. Some of the available material can be shared by different tasks. For example, Tips for writing a good lab book are common to both the technical and scientific evaluation and the commercial and regulatory evaluation. The purpose of this is to highlight that this matter is important for the three types of evaluation. The available material is found collected in the last chapter

of this book or through QR code when available. You can also consult the BIC Best Practice Handbook, available for free in our website.

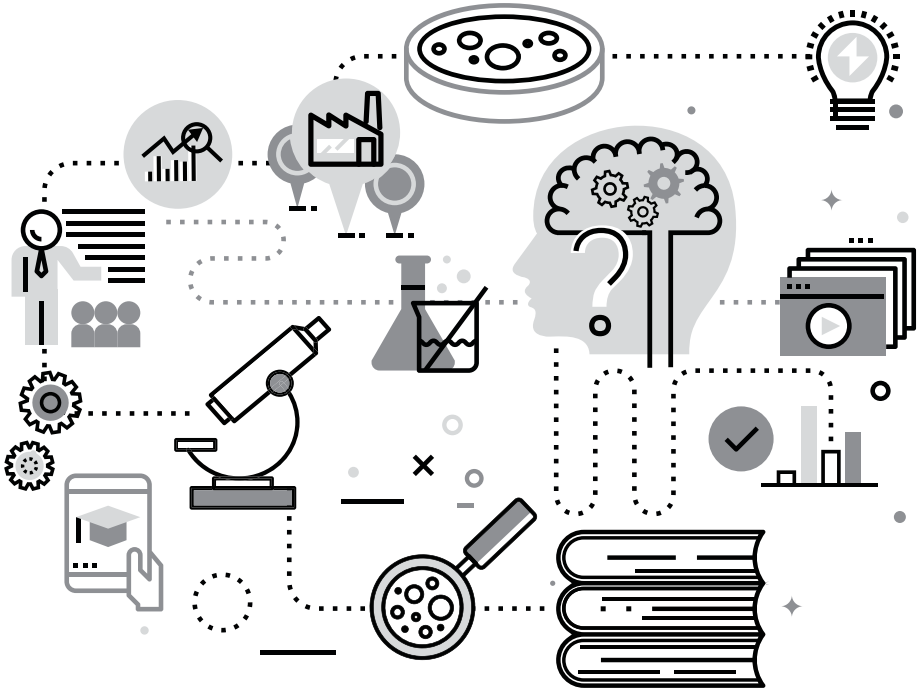
The chapters end with a **self-evaluation** checklist, where you will find a series of relevant or essential questions specially oriented towards the clinical need, the market and the feasibility of your intended product. We would like to highlight that these questions are actually the same you will find in the Review tool on our website, a checklist that is greatly recommended to follow with your technology transfer officer or your project manager.

A final recommendation that we give is that until you haven't developed a strategy for securing your Intellectual Property, do not publish, share, present or disclose your discovery. Doing so could severely restrict the scope of and the ability to patent and commercialize your invention.

I. RESEARCH STAGE

1. DISCOVERY PHASE

Biomarker Discovery
TRL-1 Basic principles observed



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PHASE DESCRIPTION

Review of scientific knowledge base

Initial literature and experimental research using qualitative or semi-quantitative methods with selected sample matrices leading to the basic principles of putative new biomarker(s)

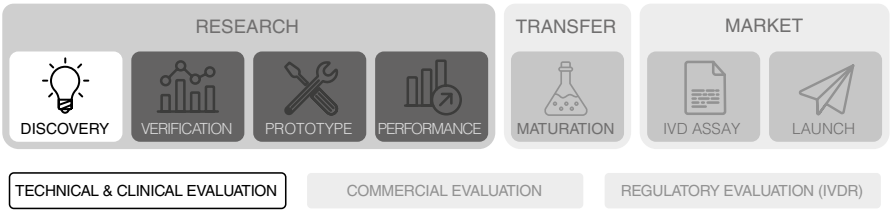
Assessment of basic analytical consistency, statistical significance and scientific validity of results confirmed

First assessment of novelty

Hypothesis formulated and techniques selected for scientific validation (proof-of-principle) studies

Early commercial research on potential use case

I.1.A. DISCOVERY: TECHNICAL AND CLINICAL EVALUATION



TASK 1. PURPOSE OF RESEARCH AND STUDY DESIGN

The two key outputs of this stage are a tentative/first draft of a study/research plan and analysis of alternative/competing methods. The later will form the basis for your competitor analysis as part of your commercial development.

- Define the specific disorder, condition or risk to be analyzed.
- What is the clinical question to be solved?
- Search for solutions and information in peer-reviewed scientific literature, patent databases and commercial applications (existing or under development).
- Consider biomarkers belonging to different molecular classes and different analysis methodologies.
- Document the gold standard method currently used in the clinical practice whether it is an imaging approach or a laboratory test.
- Take into account possible different clinical viewpoints in different countries.
- Compare all the potential biomarkers and technologies for the same use/indication.
- Identify gaps that could be solved with better markers and/or in vitro diagnostic (IVD) products.
- Take into account potential limitations coming from existing intellectual property rights (IPR).
- Create an early/rough study design and describe the analysis method(s) employed.
- Set the hypothesis (the clinical question) to be answered.
- Describe the clinical study type (e.g. paired case-control study or cohort study) and provide full descriptions of the clinical specimens analyzed, including n (specimens), n (independent cohorts), specimen matrix, selection criteria

(both for specimens and specimen matrices), storage conditions and time of storage, level of representativeness of the entire target population (special attention to biases in case of case-control pairing or enriched proportion of positive specimens!), geographical coverage and other demographics.

- Evaluate the probability for inherent bias and describe the actions you have taken to control it.

RELATED TASK:

STAGE: Transfer – **PHASE 5:** Maturation
Technical and Clinical Evaluation

▶

TASK 1
Biological characteristics of the biomarker

TASK RELATED (EXTERNAL) LINKS:

International Medical Device Regulators Forum (2019), Clinical Evaluation – Appendix B: A Possible Format for the Literature Search Report, p. 21-22.
http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

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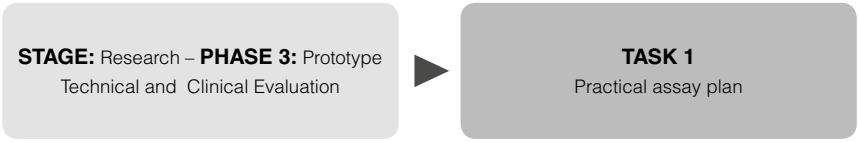
AVAILABLE MATERIAL: BEST PRACTICES ON PATIENT CONSENTMENT

TASK 2. FIRST STATISTICAL EVALUATION OF RESULTS

- Calculate the p-value for the putative findings (ideally below < 0.05, if not what are next steps in getting acceptable statistics?)
- Calculate the effect size (quantitative difference) and confidence intervals when feasible, i.e. when a quantitative analysis method has been employed.
- Are the differences detected clinically meaningful or not – Begin to consider clinical decision making: who will act on the information provided? Is there significant priority overlap between the groups that would make clinical decision making impossible?
- Evaluate the clinical concentration ranges detected: Could the range be accurately measured with a practical, routine-applicable assay.

RELATED TASK:



TASK 3. DESCRIPTION OF THE PUTATIVE BIOMARKER(S) FINDING

- List the names of the putative new biomarker(s) identified (f.ex by an omics study or other). Include all synonyms/acronyms and codes both at the gene and transcript (mRNA, protein) level.
- Describe the applicable molecular forms for measurement (DNA, RNA, protein, glycovariant, metabolite etc.).
- Define the anatomic organ of origin and the specimen matrices (e.g. serum, plasma, embedded tissue, urine, saliva, etc.) proposed as suitable for analyzing the biomarker.
- Estimate the clinically relevant concentrations in the suitable specimen matrices and list the applicable analytical method(s) accordingly.

TASK 4. REVIEW OF THE LITERATURE FOR THE BIOMARKER

- Search for information available on the putative biomarker(s) finding(s) in peer-reviewed scientific literature and patent databases and where possible commercial applications.
- Make an overview of the previously published methods (including those for alternative molecular forms), intellectual property and results obtained previously.
- Consider:
  - **a.** What is the specific association between the biomarker and the disease: is it known or can it be hypothesized?
  - **b.** Are there any associations to other diseases or benign conditions?
  - **c.** Is the biomarker elevated in alternate situations (e.g. due to systemic response or cellular stress) or is it specific to the condition investigated?
- Apply the information when planning the biomarker verification studies. For established/published biomarkers, also consider how your discovery improves current understanding, processes, etc. (i.e. what is the value of the discovery?)

TASK 5. CONSIDERATION FOR A PANEL OF BIOMARKERS (BIOMARKER SIGNATURES)

When working on a panel of biomarkers:

- Consider the quantity of data or confirmatory tests you need to collect/perform before you are able to pick the top biomarkers for further studies.
- What is the minimum panel required to achieve the same result/accuracy/precision/significance/etc. as the full panel you are exploring?
- Evaluate differences between the relevance of the biomarkers. Are some more associated with the disease than others? Perform a pathway analysis to define how the biomarker is related to the condition of interest.
- Consider if your multiplex assay could be simplified to use biomarkers of the same molecular class so that multiple analytical methods and sample preparation methods could be avoided.
- Are the concentrations to be used in the assay relevant for clinical sample collection or are several specimen preparation or analytics methods required? Is there a path forward to simplify this process?
- Evaluate the complexity of result interpretation required. Could a computer algorithm be developed for result interpretation or are manual decision trees required? Is a sequential personalized testing scheme required?
- Considering available methods/practices, how transparent and understandable (= acceptable) is the method to a clinician?

TASK 6. PRELIMINARY STABILITY STUDIES

It is likely that at this point of research, you are working with retrospective samples. If so, consider:

- Is a record readily available of how samples have been stored?
- Has prior storage/handling had any influence on the observed results?
- As a next step, validate the results using fresh samples:
  - **a.** How do findings from fresh samples agree with the retrospective samples?
  - **b.** If significantly different, consider/study the impact of different storage conditions including (temperature, light, etc) and impact of other procedural steps such as multiple freeze-thaw cycles.

Upon completion of the above:

- Assess, how stable is the biomarker?

- What is the percentage of recovery by making dilutions of either a high-concentration specimen or a standard preparation in a fresh specimen matrix (negative or low sample). Can you measure the amount added? If not, consider if the biomarker becomes bound, nicked or degraded in a fresh sample and if it is stable enough for the planned clinical analysis.

Apply all of the above information when planning the verification experiments of Phase 2.

TASK 7. TYPE AND PURPOSE OF THE FORESEEBLE IVD TEST

- Describe the purpose of the foreseeable IVD test: What is the test used for and what is the specific disorder, condition or risk to be analyzed?
- Describe the type of the test:
- Diagnostic, prognostic, predictive (for which therapy?), screening, risk/susceptibility, companion diagnostics (for which drug?), or some other?
- Will the test be able to detect the disease at an early stage (before clinical symptoms or directly after onset of the disease)?
- Can the disease be successfully treated at the time of a positive test result?

TASK RELATED (EXTERNAL) LINKS:

Global Harmonization Task Force (2012), Clinical Evidence for IVD Medical Devices / Clinical Performance Studies for In Vitro Diagnostic Medical Devices – Appendix, pp. 18.
http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n8-2012-clinical-performance-studies-ivd-medical-devices-121102.pdf

TASK 8. POSITIONING THE TEST IN THE CLINICAL CARE PATHWAY

- Describe the current clinical care pathway (what is tested and when) and how the test/assay/analysis being developed would fit into this pathway/workflow.
- Consider:

a. Does the test depend on results from other methods (i.e., an "add-on test"), or is it a "stand-alone test" with no preceding or confirmatory testing required?
b. Will it replace or complement an existing test, if so which one?
c. What are the advantages of/reasons for using this test to existing alternatives?
d. Is there risk for over/under-diagnosis? What is the consequence of each to the patient, doctor and health system?
e. Does the test help mitigate, reduce risk of mortality?
f. Does the test generate contradictory results to currently established methods? If so, why/how can this be rationalized/understood?

TASK 9. CLINICAL NEED

Describe the significant, unmet medical need the test addresses.

- What are the existing therapies (or means of prevention) for the disease of interest?
- How does the result of the new test alter the treatment of the patient and how can/will it improve the patient outcome?
- How do the tested patients fare better compared to untested patients?

Consider starting dialog with clinicians early and acquire written feedback for the suggested application. How does this feedback influence your product concept and your technical development plan?

AVAILABLE MATERIAL: BEST PRACTICES ON THE DEFINITION OF THE CLINICAL NEED, CLINICAL UTILITY AND CLINICAL BENEFIT

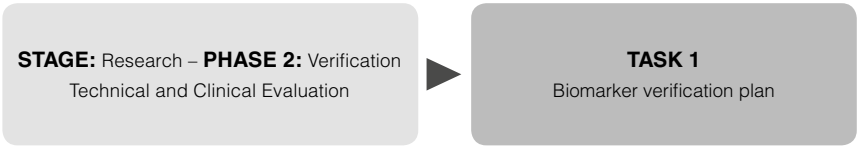
TASK 10. CONSISTENCY OF THE RESULTS

Collect evidence for the consistency of the results by:

- repeating the analyses,

- increasing the sample size (e.g. by additional sample cohorts with a wider geographical/ethnical coverage) and
- preferably having the results confirmed by other research sites.

RELATED TASK:



TASK 11. DOCUMENTATION

Good documentation of your work will play an important part in securing intellectual property, regulatory approvals, discussions with potential partners and overall technical development. As such, it is advised to:

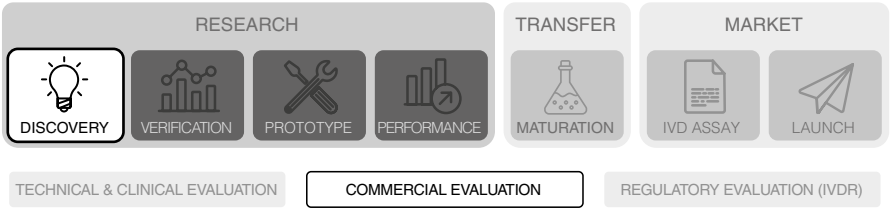
- Keep track of all experiments in a laboratory notebook (consider a digital one).
- Take time to update the notebook after each activity. It is an official document that will be needed later on.
- Keep all raw data well-stored.
- In all documenting, follow the spirit of Good Laboratory Practices, Good Scientific Practice and Good Documentation Practice to the extent possible. These practices will help in ensuring high quality in experimenting (e.g. sufficient number or replicate reactions) and documenting (all relevant materials, conditions and other parameters).
- Use an organized page layout (template) to save time, improve readability and consistency.
- In addition to the experiment purpose, write down the main conclusion of the experiment in the Title (in one short sentence, similarly to when writing a title for a scientific paper).
- If possible, from project start use a suitable experiment numbering system, where related experiments can be sorted and linked.
- Create a numbering system also for the reagents and tools produced by your own experiments, so that all experimental products have a unique ID.
- For commercial reagents, document at least the full name, manufacturer, order code, lot number, expiry date and storage conditions.
- Document the pH and contents of all buffers and reactions.

- Document actual conditions such as numerical temperatures instead of "Room Temperature (RT)" for storage or incubation.
- Document all instruments and instrument parameters (e.g. columns, filters, run parameters, measurement parameters, and wavelengths) similarly and carefully.
- Document all results and observations, including any unusual ones.
- Freely use illustrations, photos (e.g. of the setup) drawings, plots and tables for added clarity.
- Date and sign new pages after each experiment/workday.
- Make intermediate reports at specific milestones (when/if these have been identified).
- Apply the achieved knowledge in planning the next tasks and phases.

PAY SPECIAL ATTENTION TO: To secure intellectual property rights, keep the results confidential until the results have been confirmed and the novelty and patentability surveys performed. If you haven't already contact the technology transfer office (TTO) of your organization for any questions. (If unavailable, consider meeting a third party TTO to help you in the process) Note that abstract, posters, conference presentations and interviews count as publications.

AVAILABLE MATERIAL: TIPS FOR WRITING A GOOD LAB BOOK

I.1.B. DISCOVERY: COMMERCIAL EVALUATION



TASK 1. DESCRIBE THE CLINICAL NEED AND UTILITY FROM A COMMERCIAL POINT OF VIEW

If you have not already begun to do so, consider what problem your test will address and how will it be positioned in the clinical care pathway:

- What unmet, significant clinical need would the test solve?
- How does the test results affect treatment of patient and improve patient outcome?
- How do the tested patients fare better compared to untested patients?
- Do you have documented opinion of suggested end users?
- Is the diagnosis actionable, i.e. are there preventive steps to be taken if diagnosis is established or an existing therapy?
- Without an existing therapy, what is the value of the diagnosis?
- If no therapy exists, can the method be used in the development of novel therapies?

AVAILABLE MATERIAL: TIPS FOR WRITING A GOOD LAB BOOK

TASK 2. PREPARE A DEVELOPMENT PLAN

If you are working without a commercial/business development counterpart in your organization/team, this is the point at which to approach your organizations Technology Transfer Office (TTO) or someone with commercial experience to begin to plan project milestones and timelines.

In these discussions you should:

- discuss key activities,
- plan for resource needs (time, skills and materials),
- discuss how the above could/should be funded.

TASK 3. FUNDING PLAN

Based on discussion with your commercial counterpart/TTO develop a funding plan:

- How far can the research be taken with current/own funding?
- Are there specific funding sources you have access to?
- What are the relevant funding sources (e.g. innovation funds, charities, large company foundations, European programs, venture capital)?
- Is interest in furthering the project secured and supported by your organization?

TASK 4. COLLABORATION PLAN

Develop a collaboration/team plan for the project, if needed:

- Does the project require specific expertise that the team lacks?
- If so, have you established where this expertise is situated? Have you or do you need assistance with establishing contact?
- Does the project require clinical specimens/instrumentation/other that are not currently available?

TASK 5. SUMMARIZE YOUR RESULTS IN A LAYMAN WAY FOR PREPARING A DECLARATION OF INVENTION

Begin laying the groundwork for securing the resulting intellectual property of the project. If you have not done so at this point, take an introductory meeting with a patent lawyer.

In preparation identify and where possible prepare/document:

- the novelty of your results
- background for the invention (e.g literature references and patents/technologies identified to date)
- possible end markets/applications for your biomarker/invention

Communicate/repeat this discussion with your TTO.

RELATED TASK:

STAGE: Research – **PHASE 2:** Verification
Commercial Evaluation

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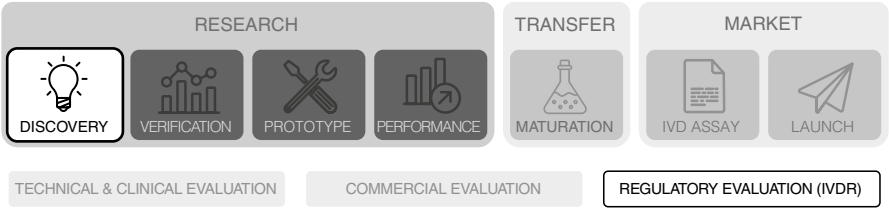
TASK 6
Report your invention to the TTO

AVAILABLE MATERIAL: TIPS FOR A GOOD DECLARATION OF INVENTION

I.1.C. DISCOVERY: REGULATORY EVALUATION



TASK 1. FAMILIARIZE WITH GENERAL INFORMATION REGARDING STAGES OF DEVELOPMENT FROM THE REGULATORY PERSPECTIVE.

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

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

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 2. CONSIDERATIONS FOR ETHICAL APPROVALS FOR USING BIOLOGICAL MATERIAL

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

- Check if you have the appropriate and current approvals for the use of data, material, samples etc. to start your project.
- Consider if you are planning on transnational/cross-border exchange of samples. If yes, additional requirements could arise.

Consider what is the standard and if there is a difference between applying for ethical approval for a whole research project or single medical experiment. These requirements can vary significantly across nations/regions.

TASK RELATED (EXTERNAL) LINKS:

Ethics Issue Table – Checklist
http://ec.europa.eu/research/participants/portal/doc/call/h2020/msca-rise-2014/1597696-ethics_issues_table__checklist_en.pdf

AVAILABLE MATERIAL: BEST PRACTICES ON CLINICAL SPECIMENS

TASK 3. CONSIDERATIONS FOR PATENT FILING

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.

TASK 4. GOOD PRACTICES (PHASE 1)

Regulatory approval requires specialist knowledge given the breadth and depth of regulatory practices currently in place in the industry (e.g. IVD development standards, GLP, FAIR, QPBR, CMS/CLIA, etc.)

- As a first point, consider how and who should handle these various procedures. The key responsibility of the researcher will continue to be conducting well documented experiments.
- Review your plan for data collection, storage and recording. (See Section Biomarker Discovery – Guide for biomarker development – technical and clinical performance Task Documentation for suggestions on best documentation practices) Regulatory approval agencies certify only those IVD medical devices which are backed by reliable data generated by the researcher/would-be commercial entity in accordance with IVD standards. Failure to comply with these standards may result in requests for new data.
- Where possible, research should be carried out in conformity with current standards and IVD methods. It is recommended to implement a quality system and/or a data management & stewardship system e.g. GLP, FAIR.
- Work according to a quality system for non-clinical studies. Familiarize yourself or a member of your team with popular standards and norms: e.g. QPBR, GLP, FAIR (for scientific data management and stewardship.)

TASK RELATED (EXTERNAL) LINKS:

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

U.S standards: CMS/CLIA: In the U.S quality control of laboratory process, requirements for technicians and proficiency are under CLIA regulation. Compliance with CLIA standards are not obligatory in EU, but provide comprehensive standards in field. More information can be found here:

Centers for Medicare & Medicaid Services
https://www.cms.gov/regulations-and-guidance/legislation/clia

FDA: Clinical Laboratory Improvement Amendments (CLIA)
https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia

Clinical and Laboratory Standards Institute (CLSI)
https://clsi.org/

European Standards by European Committee for Standardization,
https://standards.cencenelec.eu/dyn/www/f?p=CEN:105::RESET::::

e.g.
EN 13612:2002 "Performance evaluation of in vitro diagnostic medical devices"
https://standards.cencenelec.eu/dyn/www/f?p=CEN:105::RESET::::

AVAILABLE MATERIAL: TIPS FOR WRITING A GOOD LAB BOOK

PHASE ACHIEVEMENTS

Report of basic principles observed

Assessment of **statistical significance*** performed

Initial survey of scientific knowledge base and linkages between marker and disease completed

Tentative development plan drafted

Tentative commercial approach in-place, including: potential funding sources, partners, options for position in clinical pathway, understanding of alternative technologies/biomarkers/platforms/etc. for competitive awareness and or collaboration

Raised awareness of potential regulatory requirements, especially pertaining to documentation of results

Any gaps, in documentation processes identified and steps identified/taken to address these gaps

* **statistical significance**: the likelihood of a difference being observed due to chance. It does not give information on the scale or direction of the difference.

SELF-EVALUATION-DISCOVERY PHASE

CLINICAL NEED

Is the clinical need sufficiently identified and described?	☐ YES	☐ NO
Have you performed initial statistical significance evaluation of the putative findings and clinical meaningfulness?	☐ YES	☐ NO
Do you have prepared a plan for testing the consistency of the results and stability?	☐ YES	☐ NO

MARKET

Do you recognize a potential market for your biomarker? does it fill a gap or otherwise improves current testing scheme?	☐ YES	☐ NO
Would your biomarker or biomarker panel improve the current gold standard? (if yes, is the effect of the improved clinically significant?	☐ YES	☐ NO

FEASIBILITY

Can you secure access to clinical specimens for further studies and whether existing ethics approvals cover further work?	☐ YES	☐ NO
Have you made a proper survey on novelty and potential limitations from existing IPR (prior art)?	☐ YES	☐ NO
Do you know, how to finance further steps of commercialization?	☐ YES	☐ NO

I. RESEARCH STAGE

2. VERIFICATION PHASE

Biomarker verification and preliminary scientific validity studies

TRL-2 Proof of Principle Studies

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PHASE DESCRIPTION

Scientific validation via further data gathering using quantitative analyses, increased sample size, parallel testing sites and wider population coverage

Increasing biological knowledge of the biomarker and its basic analytical features

Assessment of **clinical significance*** by statistical analysis

Feature identification of a potential practical assay application for proof-of-concept studies

Clinical need and clinical utility confirmation, including assessment of the benefits and market potential of the suggested novel **IVD*** assay

Aggregation of technical surveys into commercial competitor analysis

Meetings with potential users/customers for feedback/ ideas

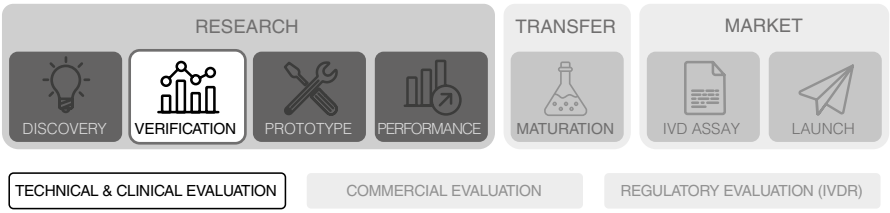
Preparation of early commercial materials for finding future partners, investors and early employees (if relevant)

Building familiarity with regulatory standards and practices

***clinical significance:** The practical importance of a scientific observation. It is used as a tool to quantitatively assess whether the magnitude of an observed difference is such that it is relevant to patients. Measures include e.g. effect size and risk ratios.

***IVD**: Test (assays) used for in vitro examination of clinical specimens derived from the human body to provide information on the health status of the subject.

I.2.A. VERIFICATION: TECHNICAL AND CLINICAL EVALUATION



TASK 1. BIOMARKER VERIFICATION PLAN

Continuing with the work initiated in phase 1 *Biomarker Discovery* – Technical and Clinical Evaluation, Task: Consistency of Results, the scope of the study/sample collection should be expanded, consider:

- To establish a plan for verifying the biomarker finding(s) using quantitative confirmatory analysis methodology and additional specimen cohorts with an increased diversity that better covers the potential target population.
- To decrease the extent of specimen picking and increase the proportion of negative specimens.
- Describe the study design and the analysis method(s) employed.
- Describe the clinical study type and provide a full description of the clinical specimens analyzed.
- Start increasing the geographical coverage to the extent possible.
- Identify and review inherent bias in the study design and describe the actions you have taken to control it.
- Prepare a statistical analysis plan.

PAY SPECIAL ATTENTION TO: Ethics committee approvals and patient consents.

TASK 2. CONSISTENCY AND REPRODUCIBILITY OF RESULTS

Evaluate the consistency and reproducibility of results between sample cohorts, analyses, operators/instruments and methods in-house and between-site (where available).

- Are the same observations made repeatedly?
- What is the level of variation between the analyses?

TASK 3. STATISTICAL ANALYSIS AND EVALUATION OF CLINICAL RELEVANCE

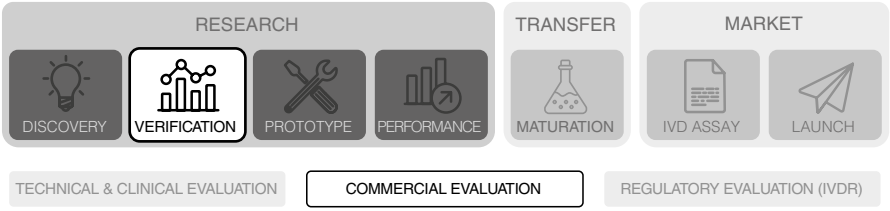
- Re-calculate the p-value (ideally below < 0.05 for continuing, if not what steps can be taken to get to this level).
- Calculate the effect size (quantitative difference) and confidence intervals when feasible i.e. when using a quantitative analysis method.
- Based on your conversations with clinicians and practitioners, re-consider whether the differences detected are clinically meaningful and would allow for clinical decision-making.
- Note that a significant overlap between case and control groups would make clinical decision-making impossible despite of the p-value (i.e. resolution) achieved.
- Consider also if the clinically relevant concentration range could be accurately measured using a practical (routine-applicable) assay.

TASK 4. SPECIFICITY OF THE BIOMARKER TO THE DISEASE

Revisit and – if possible – expand on the biological link of the biomarker to the disease:

- Is the biomarker disease-specific or does it have a shared molecular pathology across diseases?
- Is the biochemical pathway known?
- Is the biomarker elevated in any benign conditions?

I.2.B. VERIFICATION: COMMERCIAL EVALUATION



TASK 1. GET FEEDBACK FROM CLINICIANS/CLINICAL LABORATORIES

General interest of healthcare professionals (clinicians, laboratories) and companies in the IVD field needs to be confirmed on a non-confidential level, preferably in several areas. Make a written report on the feedback you receive.

If possible, consider drafting legally non-binding letters-of-intent (LOI) reflecting clinicians and practitioners need for and willingness to use the proposed "diagnostic".

TASK 2. TARGET POPULATION

- Revisit and -if possible- expand on the relevant target population:
- Male/Female?
- Certain age group?
- Apparently healthy, symptomatic, having a risk, or readily diagnosed?
- Certain subgroup of the sick?
- Which ethnicities?

TASK 3. PREVALENCE OF CONDITION IN TARGET POPULATION? PREDICTIVE, DIAGNOSTIC OR MONITORING TEST?

- Give the yearly incidence of new cases/100,000.
- What fraction of cases or the population is to be tested?
- Based on disease rates in different geographic regions, present estimates of the number of tests that would be performed yearly.

TO BE CONSIDERED: As a rule of thumb, the business case for tests targeting patients who are either already diagnosed and or have a rare disease, is markedly lower than for tests e.g. for all symptomatic patients. Reconsider, the value created by the biomarker/

diagnostic, what new information is added, what clinical challenges removed and are these improvements for instance 10 times better than current methods?

TASK 4. ANALYSE THE COMPETITIVE LANDSCAPE AND MAKE A STAKEHOLDER REVIEW

Using information gathered from your search of publications, patents and commercially available products:

- Begin to list companies providing diagnostic solutions for the condition of interest, expanding on your understanding of potential competition.
- Consider performing this task in conjunction with your Technology Transfer Office/commercial development officer.
- Update or make an overview of potential collaborators, commercial partners and competitors (scientific teams, companies, clinical laboratories, etc.).

AVAILABLE MATERIAL: TIPS ON CONDUCTING A COMPETITION ANALYSIS

TASK 5. CONDUCT A NOVELTY AND PATENTABILITY ANALYSIS

Protection of intellectual property is a key consideration for funding agencies to support further development. If you have not done so, meet with a patent lawyer to discuss how the ability to patent may be impacted by existing public information (prior-art).

- In preparation for this meeting consider/prepare:
  - **a.** Novelty is the first major pre-requisite for patenting: Has the biomarker or its use in the intended indication, previously been published by the inventors or by a third party? Perform a prior-art search in both scientific and patent databases. Consider hiring the patent firm to further expand on this prior-art search.
  - **b.** Inventiveness is the second major pre-requisite for patents: Does analysis of the biomarker result in an unprecedented technical effect, such as unexpectedly informative result that is not achieved by competing methods? Describe the significant improvements compared to existing markers and methods. What problem(s) is/are solved?
- Prepare key references that a patent attorney can study to further/expand the analysis.

CONSIDER: A space with extensive patent protection may harm the potential of developing a business. Be prepared to re-consider alternative conditions.

AVAILABLE MATERIAL: MAIN PREREQUISITES OF PATENTING

TASK 6. CAN YOU DOCUMENT, JUSTIFY OR EXPLAIN THE SPECIFICITY TO THE TARGETED CONDITION?

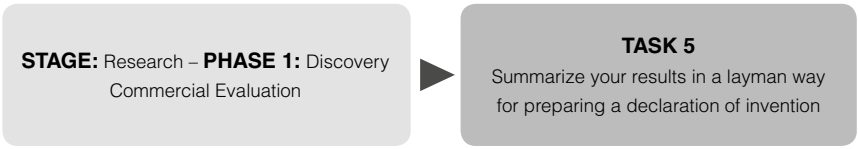
Review, and if possible, expand on further:

- Is the biomarker disease or condition specific? Or does it have a shared molecular pathology across diseases?
- What is the link between the marker and the biochemical pathway of the disease/condition?

TASK 7. REPORT YOUR INVENTION TO THE TTO.

If not already done, report your invention (also described under phase 1 "Biomarker Discovery" – Commercial Evaluation, Task: Summarize your results in a layman way for preparing a declaration of invention).

RELATED TASK:



AVAILABLE MATERIAL: TIPS FOR A GOOD DECLARATION OF INVENTION

TASK 8. REASSESS PARTNER NEEDS FOR THE NEXT PHASE

Revisit/reflect on your partner and sample/material acquisition strategy:

- Do you have access to relevant samples in necessary quantities?

- Do you require development of specific antibodies?
- Who are collaborators, institutions and companies that can help you in this?

TASK 9. PLAN FOR A PATENT STRATEGY

As your patent advisor may have made you aware, there is a 12 months window between submission of an initial claim and full patent application. To assure sufficient content in the application, it could be in your interest to postpone filing, especially if there is no urgency to publish scientific results. Based on commercial discussions and market research begin outlining a patent strategy.

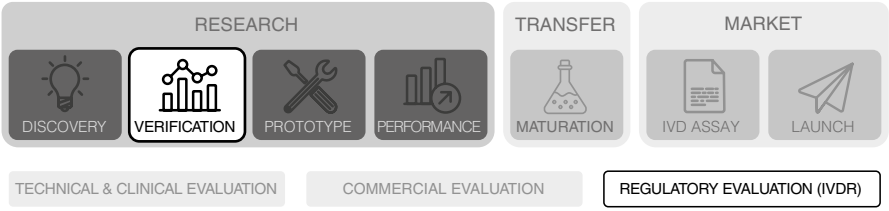
CONSIDER:

- The time for drafting a solid application ranges between 2-3 months.
- How will the presence/absence of a patent impact your discussions/ collaboration with potential/desired partners?
- Are any of the competitors working on securing IP in the space?
- Based on your geographic survey of the disease/condition, what are geographic regions of interest?

TASK 10. PREPARE A NON-CONFIDENTIAL TECHNOLOGY PRESENTATION

Having submitted an initial patent application, prepare a non-confidential slide deck/ presentation to facilitate discussion with potential/existing partners and investors.

I.2.C. VERIFICATION: REGULATORY EVALUATION



TASK 1. REVISIT REGULATORY STRATEGY

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

- What standards are relevant for your geographies of interest?
- Who will oversee the regulatory process in your team/organization?
- What standards of best practice have you/should you implement? Application of industry best practices from an early stage should smooth later stages of commercialization and interactions with regulatory agencies and partners.

TASK 2. REVISIT GOOD PRACTICES

Review and implement good practices from Phase 1.

PHASE ACHIEVEMENTS

Proof-of-Principle report completed with assessment of clinical significance

Specificity for intended condition confirmed

Survey of novelty (prior art search) completed

Declaration of invention coinciding with tentative patent strategy and or application made

Further development plan drafted

Publication plan including patent application strategy drafted

Commercial development plan drafted/refined including: estimate of potential market, number of potential users, feedback from potential users and more thorough analysis/understanding of the competitive landscape

Non-confidential presentation on commercial concept for presenting to partners and or potential investors made

Continued refinement of experimentation/ documentation practice looking forward to regulatory specifications

SELF-EVALUATION-VERIFICATION PHASE

CLINICAL NEED

Are your results consistent, reproducible and significant?	☐ YES	☐ NO
Is the biomarker specific to the disease?	☐ YES	☐ NO
Do you have enough interest from health-care professionals?	☐ YES	☐ NO

MARKET

Have you defined in detail your target population and your target product profile?	☐ YES	☐ NO
Have you analyzed the competitive land-scape? what are the products addressing the same aim and how competitive is your potential test?	☐ YES	☐ NO
Do you have positive, documented feed-back from clinicians / clinical laboratories on need?	☐ YES	☐ NO

FEASIBILITY

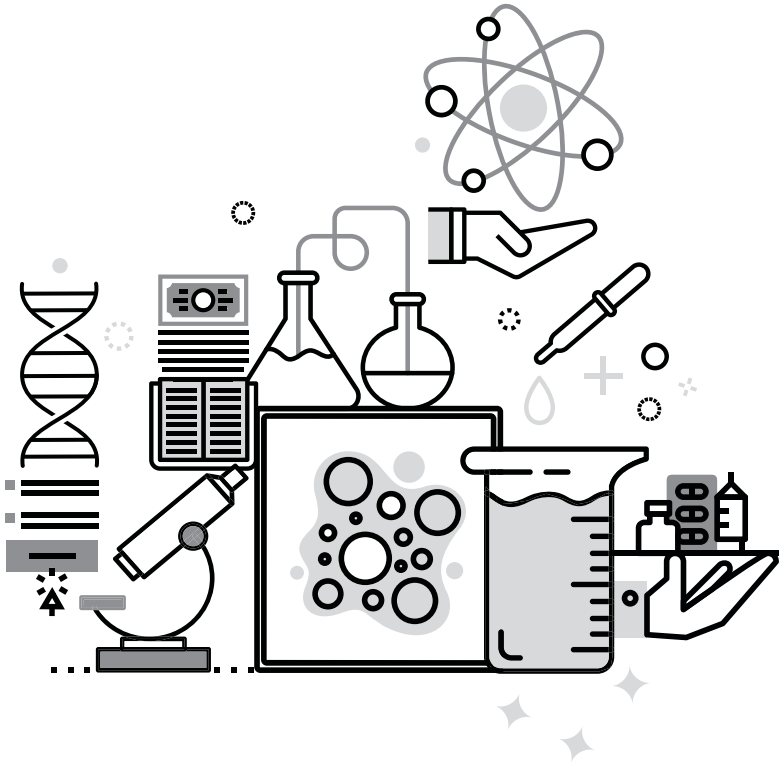
Is assay for biomarker / correlation inven-tive and patentable?	☐ YES	☐ NO
Are results consistent and scientifically valid in quantitative analyses?	☐ YES	☐ NO

I. RESEARCH STAGE

3. PROTOTYPE PHASE

Development of a specific biomarker assay (prototype)

TRL-3 Proof of Concept assay established



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PHASE DESCRIPTION

Setup of a specific prototype assay in research laboratory setting

Identification of key components and optimization of the assay

First assessment of freedom-to-operate (FTO) of methodology and components selected

Assessment of the analytical performance characteristics with spiked (mock-up) specimens in appropriate sample matrices

Early assessment of practicability characteristics and feasibility to automation

Robustness study, testing ranges of the different components

Defining System Suitability Test (SST) requirements

Early Business plan drafting outlining value propositions, competitors and customers

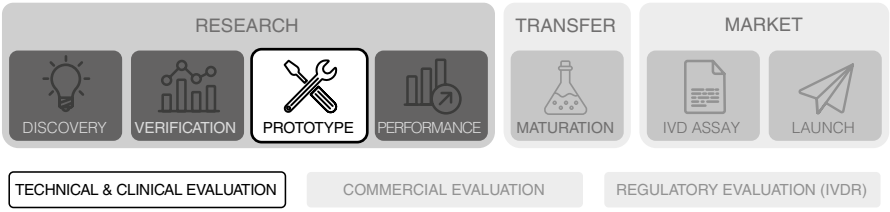
Patent analysis to support potential commercial opportunities

Drafting of early legal documents such as **CDA***, NDA

Design and approval of protocols for clinical study

***CDA:** Confidential Disclosure Agreement. Agreement defining the confidentiality terms between two or several parts in a collaboration.

I.3.A. PROTOTYPE: TECHNICAL AND CLINICAL EVALUATION



TASK 1. PRACTICAL ASSAY PLAN

Begin to plan for 'real-world' validation of the bench/lab Proof-of-Concept studies:

- Describe the assay/instrumentation for developing an IVD- assay, i.e. a first prototype.
- Where possible, look for technologies/methods routinely implemented in clinical practice. (Revisit your prior discussions with clinicians and other end-users for suggested methods/technologies/etc.).
- For specific requirements not readily met by available methods/instruments, outline the technical specifications required and identify potential suppliers. If ready, proceed to order.

TASK 2. INTERNAL AND EXTERNAL CONTROLS

Design all internal and external controls required in the Proof of Concept assay:

- For specimen preparation, co-extracted internal controls may be added into patient specimens to monitor for the success of the extraction or concentration protocol.
- For sample analysis (especially in case of nucleic acid amplification assays), an internal control is a necessity to monitor for the success of the amplification reaction and for the presence of assay inhibitors.
- External controls (such as standard preparations or characterized clinical specimens) are required to calibrate the assay and perform regular quality control on results obtained.

TASK 3. BUILDING AND OPTIMIZATION OF THE PROTOTYPE

Set up the prototype and optimize the reagents and assay conditions:

- Design the result calculation parameters and principles. Note: base all applicable calculations (such as average, coefficient of variation) on values translated into concentrations (via using a standard curve) rather than the raw signals measured.
- Assure that a statistically significant amount of replicates is used. Mimicked clinical specimens (e.g. zero samples spiked with known amounts of standard) are accepted, but always use a clinical specimen matrix instead of a simple buffer solution.

TASK 4. APPLICABLE CLINICAL SPECIMEN MATRIXES

- List the types of clinical specimen matrices that are expected to contain the biomarker(s) in sufficiently high levels.
- Select the specimen matrices used for the study.
- For invasive (biopsy) specimens, describe if the specimen is collected routinely or if the specimen is required for the current assay only. (Consider that an invasive compliment to your assay may make this an undesirable method to be used by a clinician or for a patient)
- Provide a description for any mimicked specimens that are to be used in setting up the prototype or in evaluating.

TASK 5. CLINICAL STUDY DESIGN AND CLINICAL SPECIMEN ACQUIREMENT PLAN

Design the Proof of Concept clinical study (e.g. retrospective and/or prospective cohort):

- Describe the planned target population(s) and their coverage.
- Provide the inclusion and exclusion criteria and estimate the number of specimens and independent cohorts to be analyzed.
- If not done earlier, make plans for specimen collection, preparation, storage, de-identification, chain-of-custody and disposal.
- Plan and schedule the ethics committee approvals required.
- When using retrospective sample cohorts, ensure that the patient consents allow the planned use and that there are no legal restrictions (such as agreements) that would prevent the use of the specimens.

- Provide a description and plan for the mimicked samples to be used in the analytical performance characteristics assessment of the prototype, e.g. pooled depleted clinical specimens or pooled zero-specimens spiked with a standard or a known high-concentration clinical specimen.
- Evaluate the probability for inherent bias and describe the actions you have taken to control it.

RELATED TASKS:

STAGE: Research – **PHASE 1:** Discovery Technical and Clinical Evaluation	**TASK 1** Purpose of the research and study design **TASK 11** Documentation
STAGE: Research – **PHASE 2:** Performance Technical and Clinical Evaluation	**TASK 1** Clinical specimens
STAGE: Research – **PHASE 1:** Discovery Technical and Clinical Evaluation	**TASK 6** Preliminary stability studies

TASK RELATED (EXTERNAL) LINKS:

International Medical Device Regulators Forum (2019), Clinical Evaluation – Appendix E: Some Examples to Assist with the Formulation of Criteria, pp. 24.
http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

TASK 6. ETHICAL APPROVAL APPLICATIONS AND PATIENT CONSENTS

- Follow the format suggested by the local ethical committee(s). In preparing the patient consent documents, note that the wording used dictates the use of the specimens.

- Draft the consent document early and ensure that the scope of use and field of research are not too strictly defined to allow the use of alternative analysis techniques and to target different biomarkers.
- Ensure long enough storage time to allow continuing research.
- State clearly/incorporate that the results may be used for commercial purposes (e.g. for patenting or in marketing materials) with the aim of producing new diagnostics and therapeutics.
- If possible, consult your legal department/legal advisor on the requirements of EU General Data Protection (GDPR) that apply to you.

TASK RELATED (EXTERNAL) LINKS:

Simon Fraser University – Office of Research Ethics (2017), Consent form guidelines
https://www.sfu.ca/research/sites/default/files/2019-09/2017%2004%2019%20Consent%20Form%20Guidelines%20and%20Template%20DRAFT%20FINAL.pdf

TASK 7. PREPARATION OF CLINICAL SPECIMENS

Establish the specimen preparation protocol.

- Ensure that the protocol works both in fresh and stored clinical specimens.
- For future/commercial application, consider methods to optimize the protocol at this point (e.g. decrease number of steps, using simpler methods/reagents/instrumentation)

TASK 8. ANALYTICAL SENSITIVITY

- Calculate the analytical sensitivity of the prototype assay (LoB, LoD, LoQ).
- Provide description of the clinical specimen matrix used for calculating the analytical sensitivity (e.g. pooled depleted or zero clinical specimens), the number of replicates analyzed at each concentration of the standard or calibration curve and the mathematical formula used.

TASK 9. ANALYTICAL SPECIFICITY

- Assess for the presence of any non-specific increase of signal (i.e. matrix effect) in the different clinical specimen matrices evaluated.
- Has other exogenous or endogenous interference been detected? Is the cross-reactivity (%) with closely related molecules known or can it be examined?
- Similarly, do you know what different molecular forms of the biomarker (e.g. free vs. bound; glycosylated vs. non-glycosylated; degraded or enzyme-cleaved, etc.) are measured?

TASK 10. ACCURACY OF MEASUREMENT AND LINEAR MEASURING RANGE

- Confirm the absence of or detect the presence of systematic error (bias) by analyzing reference specimens or standards with known biomarker concentrations (Trueness).
- Calculate the repeatability of measurements in terms of standard deviation (e.g. coefficient of variation, CV %) using several concentrations along the **linear measuring range.** Analyze the within-run, between-run and between-day reproducibility using a sufficient number of replicates at each measurement point (e.g. 6-12) (Precision).

TASK 11. HANDS-ON TIME, TOTAL TURN-AROUND TIME AND AMENABILITY TO AUTOMATION

Describe the manual steps and hands-on-time required for the specimen preparation and for performing the assay.

- Estimate the total turn-around time and how many specimens can be handled at the same time.
- Which steps would be amenable to automation in a clinical laboratory?
- Can a sufficiently high throughput be achieved in the routine settings to assure that all patients needing an analysis in a particular time frame receive one?
- Consider including your business partner in this to identify sources of value.

TASK 12. OTHER PRACTICAL CONSIDERATIONS

Evaluate at least the following characteristics of the prototype assay:

- *Assay kinetics:* What is the time required for a low-concentration specimen to become bound and measured >95%?
- *Presence of a high dose hook effect or prozone effect:* What concentration of analyte is required for the assay to produce a false negative result due to blocking the specific binders (e.g. capture antibodies) on the solid phase? Can such concentrations ever be encountered in clinical specimens? Can you use the prototype assay with a single dilution of the clinical specimens or are multiple dilutions required?
- *Requirement for specialized instrumentation or modified chemistries*: Consider their availability in routine clinical settings.
- *Qualitative or quantitative assay platform:* For near-patient testing, self-testing or home testing, a qualitative or semi-quantitative assay format may be sufficient and facilitate instrument-free result interpretation.

TASK 13. FINAL PROTOCOLS AND COMPONENTS

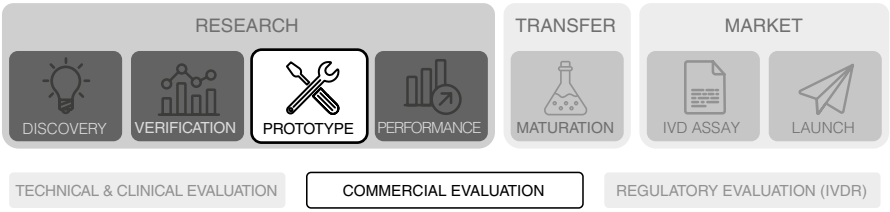
Document the optimized protocols and reagents:

- Establish a preliminary component plan where you list all the critical reagents and their specifications. Pay special attention to the specific binders such as antibodies and whether improvements (such as affinity maturation) are required or planned.
- Are there limitations in the availability (such as in the case of polyclonal antibodies or other single-batch reagents)?
- For critical commercial components, list alternative materials and sources (if any).

TASK 14. ANALYTICAL PERFORMANCE REPORT OF THE PROTOTYPE

Summarize results of the optimization and performance evaluation experiment.

I.3.B. PROTOTYPE: COMMERCIAL EVALUATION



TASK 1. DEFINE THE SCOPE OF YOUR POTENTIAL PATENT PROTECTION

Working with your patent advisor establish the scope of patent protection/panels:

- In case the test uses multiple biomarkers, can the top marker(s) be selected?
- What is the drop in **AUC** when a top biomarker is dropped out or replaced by a non-patented alternative?
- Note that sufficiently wide scope of protection is a prerequisite for patenting.

AVAILABLE MATERIAL: SCOPE OF PATENT PROTECTION

TASK 2. PERFORM A SIMPLIFIED "FREEDOM-TO-OPERATE" SEARCH

Prior to continuing toward a commercial version of your assay, it may be relevant to find out if some of your components may infringe on existing patent rights. Discuss this with your TTO officer and consider having a full "freedom-to-operate" (**FTO**) analysis performed by your patent attorney. An FTO will enable you to minimize and address any risk of patent infringement/lawsuits as you proceed further to produce/sell/import/export your new assay.

AVAILABLE MATERIAL: FREEDOM TO OPERATE (FTO) ANALYSIS

TASK 3. FORMULATE YOUR VALUE PROPOSITION

Begin to work on you customer/investor facing material, when possible with your commercial advisor.

- Translate the technical benefits/advantages of your assay/biomarker into the language of your customer. A reduction in assay turn-around time, reduced reagent use, reduced staff costs are all sources of value for patient/clinician/hospital administrator.
- Identify the specific sources of value. Why will someone choose this method over another?

TASK 4. FORMULATE YOUR COMPETITIVE ADVANTAGE

Based on the analysis of the competitive landscape, formulate your competitive advantage.

- *Competing methods:* Describe the technical and clinical performance of existing (competing) methods for the same purpose.
- *Advances of the current method:* Describe the technical, clinical and/or economic advantages (known or expected) of the new test compared to the existing methods for the same purpose. Comparison is to be purpose-oriented, i.e. independent of specific biomarkers and assay platforms. Include all competing approaches.

CONSIDER: how your technology enables you to be superior to competitors in the space. Is this a 10X advantage (If not 10X, is it a significant benefit to your customer)? How long will you be able to sustain this?

TASK 5. PRELIMINARY BUSINESS PLAN

Compile all the information that you have on the target market.

- Who will buy the tests (healthcare providers, consumers) and in what settings will they be used? By whom?
- Describe the market size, competitive positioning of the test, pricing, market barriers and risks that you foresee.
- The Business Model Canvas is a convenient model for gathering this information in one structure/document.

CONSIDER: If no price has been decided, no market estimate made, work with an advisor or seek guidance on developing these estimates. Do not focus on getting a "right" estimate. Many of these will change as the project/product matures but is needed now for further discussion with investors.

TASK RELATED (EXTERNAL) LINKS:

Riley, K. and Associates (2013), model: Business Model Canvas for Healthcare.
http://imaginego.com/overview-modelh-business-model-canvas-healthcare/

TASK 6. REVISIT THE DEVELOPMENT AND FUNDING PLANS

Revisit the development and funding plans. Based on new information re-asses:

- What do you need to do next to bring your invention closer to a commercially viable product?
- Which partnerships would you need to build and when would you need to initiate contact and dialogue?
- Plan steps for the next 12 months including budgeting, IPR and market analysis.

TASK 7. PATENTING PLAN ESTABLISHED

Plan the timing and content of a patent application, ideally with a patent attorney.

- Discuss the type and scope of patent protection and what experimental proof is required.
- A manuscript draft will serve as a good basis for drafting a patent application.
- Remember the timing of the priority year: What further proof will be available within one year?

PLEASE KEEP IN MIND NOT TO PUBLISH BEFORE THE PATENT APPLICATION IS SUBMITTED (INCL. ABSTRACTS, POSTERS, PUBLIC PRESENTATIONS).

AVAILABLE MATERIAL: HOIBERG – EUROPEAN PATENT ATTORNEYS (2020), PATENTING BIOMARKERS

TASK 8. PREPARE A NON-CONFIDENTIAL TECHNOLOGY PRESENTATION

Select information to be included in the technology presentation, preserving as much as possible any element of novelty claimed in the patent.

- Prepare the presentation to be used to start dialogue with potential partners.

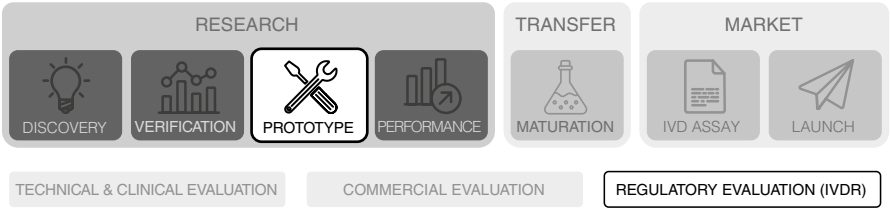
Detailed discussions should proceed only under **NDA**/ CDA/ some sort of secrecy agreement.

TASK 9. CONSIDER YOUR MOTIVATION FOR COMMERCIALIZATION

Begin to consider your future involvement in the commercialization of the technology:

- Are you ready to spend less time in the lab and more in conference rooms? Are you ready to prepare business plans and commercial marketing materials? If so, consider forming a spin-out company.
- If you are not interested in taking that role upon you, do you know people in your network that could take on that role, while you concentrate on the technical development? If so, consider forming a spin-out where you are involved in a less hands-on manner (perhaps on the board of the company)
- Do you prefer to transfer all the development work to an industrial partner? If so, consider who might be interested in buying your technology for further commercialization. Your list of competing companies is a good place to find potentially interested buyers.

I.3.C. PROTOTYPE: REGULATORY EVALUATION



TASK 1. REGISTRATION OF IVD MEDICAL DEVICE MANUFACTURER

Apply Article 26 *Registration of devices* & Article 28 *Registration of manufacturers, authorised representatives and importer*s; chapter 4.2.1 of Regulatory Guide. Proceed through the registration procedure within the EUDAMED database.

TASK 2. REVISIT GOOD PRACTICES AS PERTAINING TO REGULATORY ISSUES

The stage concerns assay lab research – no mandatory regulatory requirements to fulfill.

TASK 3. GOOD PRACTICES

Determine if the assay is under jurisdiction of the EU IVDR. Apply Article 1 *Subject matter and scope*, Article 2 (2), Article 5 (5) *Definitions* and if uncertainty exists, Article 3 *Regulatory status of products* of 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.** a physiological or pathological process or state
  - **b.** congenital physical or mental impairment
  - **c.** predisposition to a medical condition or disease
  - **d.** determine the safety and compatibility with potential recipients
  - **e.** predict treatment response
  - **f.** define or monitoring therapeutic measures.

Collect data related to analytical performance of the assay with respect to IVDR requirements Analytical performance data have to meet specific criteria as stipulated by the IVDR. Apply Annex I *Regulatory status of products*, Chapter II (No. 9.1 (a); 9.3) *Requirements regarding performance, design and manufacture* and Annex II *Technical documentation*, No. 6.1 *Information on analytical performance of the device* of IVDR.

- When planning analytical (and clinical) performance studies, remember to take into account IVDR requirements in that field. Well-structured raw data concerning specific characteristics is necessary to provide and constitute essential input for the technical documentation. The analytical performance, such as analytical sensitivity, analytical specificity, trueness (bias), precision (repeatability and reproducibility), accuracy (resulting from trueness and precision), limits of detection and quantitation, measuring range, linearity, cut-off, including determination of appropriate criteria for specimen collection and handling and control of known relevant endogenous and exogenous interference, cross-reactions.

Collect data for justification of scientific validity of further assay and apply Annex XIII *Performance evaluation, performance studies and post-market performance follow-up*, Part A (No. 1.2.1) *Performance evaluation performance studies* of IVDR.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

Global Harmonization Task Force, Study Group 1 (2011), Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices, pp. 17.
http://www.imdrf.org/docs/ghtf/archived/sg1/technical-docs/ghtf-sg1-n063-2011-summary-technical-documentation-ivd-safety-conformity-110317.pdf

Global Harmonization Task Force, Study Group 5 (2012), Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation, pp. 10.
http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf

International Medical Device Regulators Forum (2019), Clinical Evaluation – Appendix B: A Possible Format for the Literature Search Report, p. 21.
http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

PHASE ACHIEVEMENTS

- Valid biomarker(s) specific assay prototype established
- Listing of key components and optimized assay composition completed
- Key Assay parameters established (specificity, sensitivity, precision, etc.)
- Clinical study design in place
- Early assessment of all potential value propositions made, including possible quantification
- Early assessment of competition (companies, customers, value drivers) completed, summarized
- Early stage Patent analysis on risks and opportunities performed
- Confidential presentation prepared for initiating any further due diligence with legal documents to support secrecy/confidentiality (e.g. CDA, NDA)
- Continued refinement of experimentation/documentation practice looking forward to regulatory specifications
- Ethical approval of clinical study obtained

SELF-EVALUATION-PROTOTYPE PHASE

CLINICAL NEED

Have the biomarker(s) specific assay prototype been established?	☐ YES	☐ NO
Are the analytical characteristics of the prototype satisfactory enough?	☐ YES	☐ NO
Can a sufficiently high throughput be achieved in the routine settings?	☐ YES	☐ NO

MARKET

Can you formulate your competitive advantages, e.g. for a non-confidential technology presentation?	☐ YES	☐ NO

FEASIBILITY

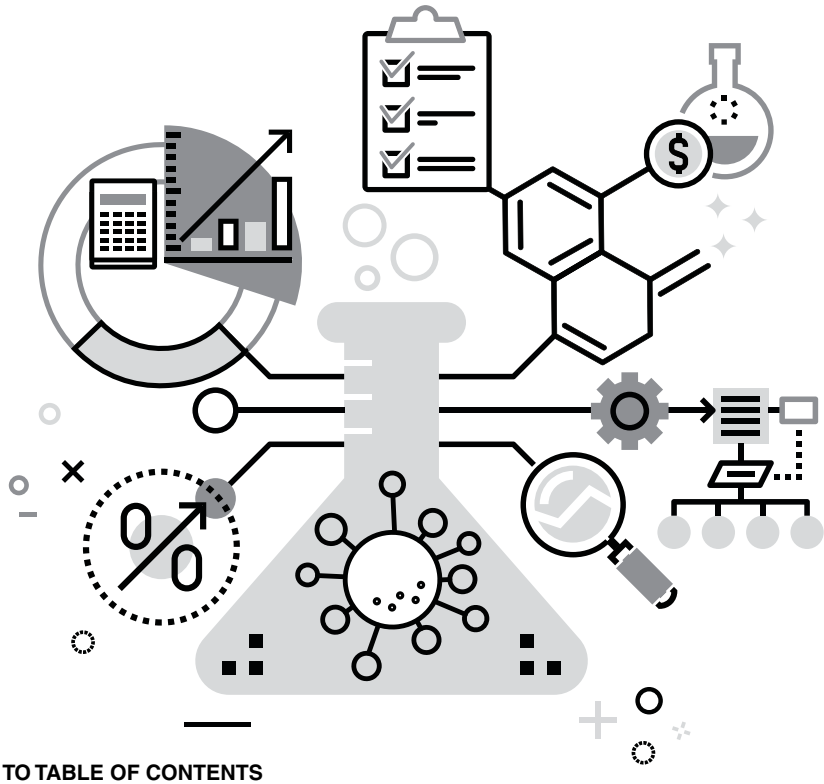
Has the freedom-to-operate search results been enabling for suggested methodology and components?	☐ YES	☐ NO
Do you have a plan for patenting of the invention?	☐ YES	☐ NO
Have you determined your assay under jurisdiction of EU IVDR?	☐ YES	☐ NO

I. RESEARCH STAGE

4. PERFORMANCE PHASE

Clinical performance of the prototype in laboratory settings

TRL-4 Proof of Concept studies with prototype assay



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PHASE DESCRIPTION

Performing assessment of clinical performance characteristics of the established prototype assay using relevant clinical specimens.

Comparing studies with golden standard methodology or comparable commercial IVD assays.

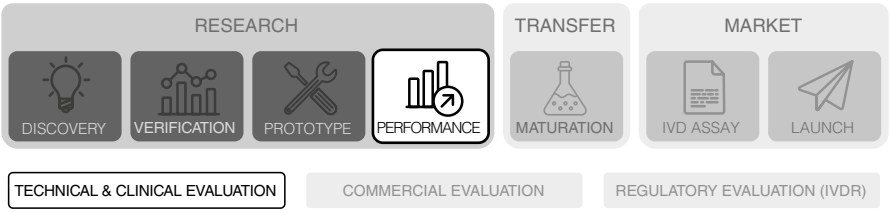
Assessing the clinical validity including precision/ accuracy in predicting the clinical condition.

Patent landscape analysis (FTO) supported and or carried out by IP partner

Articulation and quantification of value propositions

Cost Benefit Analyses for potential users/customers

I.4.A. PERFORMANCE: TECHNICAL AND CLINICAL EVALUATION



TASK 1. CLINICAL SPECIMENS

Provide a full description of the clinical specimens analyzed, including the demographics. Provide reasoning for selecting specimens for the study, as well as inclusion and exclusion criteria.

- How well do the specimens cover the target population as a whole?
- What are the gaps remaining (e.g. in geographical coverage or stage of disease detected)?

Ensure and document that all the specimen handling and storage conditions (especially all the time-critical steps) fulfill the requirements set by the earlier stability studies and specimen preparation protocols.

TASK 2. COMPARISON WITH THE GOLD STANDARD OR ANOTHER REFERENCE METHOD

- Provide a description and references for the comparison method selected. Preferably, use the golden standard (imaging method or laboratory test for the same intended use) or a well-established equivalent commercial IVD-test.
- Blinding of specimens will allow avoiding bias especially in the case of marginally positive specimens.

TASK 3. ROC ANALYSIS

- Perform a **ROC** (receiver operating characteristic) analysis.
- Calculate AUC-values (area under the curve) for the prototype and for the comparison method.

- Compare the results: Does the prototype reach the aims set for clinical performance?

TASK 4. SUGGESTED DIAGNOSTIC CUT-OFF CONCENTRATION

Calculate the optimal suggested diagnostic (clinical) cut-off concentration and rationalize it (e.g. optimal diagnostic sensitivity, optimal diagnostic specificity or overall optimal diagnostic accuracy in the ROC analysis).

- Note that the optimal cut-off value may be lower than the detection limit of the current prototype assay (i.e. lower than a concentration clearly differing from the background e.g. at conc. CV<10 % or mean blank + 3xSD). If that is the case, take efforts to increase the analytical sensitivity of the prototype.

Also:

- Document the clinically relevant concentration range detected in the specimen cohort.
- Ensure that high-concentration samples have not surpassed the measuring range of the prototype by making dilutions of at least a subset the clinical specimens.
- How well does the linear measuring range of the prototype fit with clinically relevant concentrations?

TASK 5. DIAGNOSTIC SENSITIVITY (%) AND SPECIFICITY (%) OF THE PROTOTYPE

Using the selected optimal cut-off concentration of the ROC analysis, calculate the diagnostic (clinical) sensitivity (%) and specificity (%) of the prototype.

TASK 6. REFERENCE VALUES IN HEALTHY POPULATION

Further increase the number of specimens analyzed from apparently healthy individuals.

- Retrospective cohorts are also suitable as long as the patients have not been suspected of having the condition under investigation and the sampling and specimen handling/storage conditions are acceptable.
- Carefully analyze for differences in levels detected between cohorts or populations. If false positive results are encountered, analyze the specimens first with other methods (to detect potential true positives) and then for assay interference.

TASK 7. DETECTED POSITIVE AND NEGATIVE PREDICTIVE (PPV AND NPV)

Calculate the **PPV**/ NPV (positive and negative predictive value) detected in the clinical cohort.

TASK 8. EXPECTED POSITIVE AND NEGATIVE PREDICTIVE VALUES (PPV AND NPV)

Calculate the PPV and NPV expected in the entire target population. Take into account the prevalence of the disease and the diagnostic sensitivity (%) and specificity (%) calculated for the prototype at the selected clinical cut-off concentration.

1. INPUTS:

→ Diagnostic sensitivity %
→ Diagnostic specificity %
→ Overall prevalence in population (cases / 100 000)
→ Prevalence rate in the target population (cases / 100 000)
→ Give the selection criteria for the applicable sub-population (e.g. risk, symptom, age group etc.)

2. OUTPUTS:

→ Positive Predictive Value (PPV) %
→ Negative Predictive Value (NPV) % (Either/both in unselected and selected populations)
→ False positive rate
→ False negative rate

CONSIDER if the clinical performance of the prototype is sufficient for the intended use. A low PPV or NPV require specific reasoning.

- For low PPV, is there a non-invasive confirmatory test readily available? Or is the disease very disabling and must be definitively ruled-out by the test?
- For low NPV, are there economic or ethical reasons to decreasing the number of false positives at the expense of increased false negatives?

AVAILABLE MATERIAL: CLINICAL PERFORMANCE CHARACTERISTICS

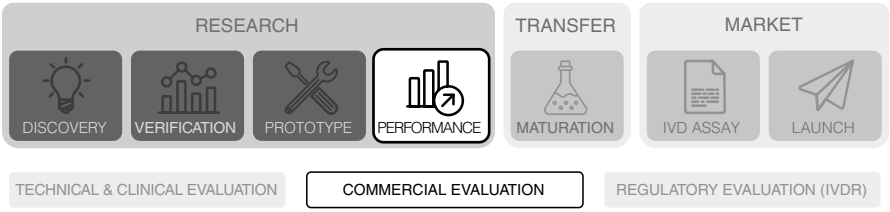
TASK 9. CLINICAL PERFORMANCE REPORT OF THE PROTOTYPE

Collection of main findings from the clinical performance studies and asses the **clinical significance**.

TASK RELATED (EXTERNAL) LINKS:

International Medical Device Regulators Forum (2019), Clinical Evaluation – Appendix G: A Possible Format for a Clinical Evaluation Report, pp. 28.
http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

I.4.B. PERFORMANCE: COMMERCIAL EVALUATION



TASK 1. POSITIONING OF THE ASSAY IN THE CLINICAL

Describe the current clinical care pathway (testing sequence) and consider where the biomarker/assay fits best:

- New steps in testing chain (if yes, where?)
- Improves current steps (if yes, which?)
- Replaces current steps (if yes, which?)

Discuss and consider with your business advisor what could be applicable business models for technology transfer.

RELATED TASK

STAGE: Research – **PHASE 1:** Discovery
Technical and Clinical Evaluation

▶

TASK 1
Positioning the test in the clinical care pathway

TASK 2. ECONOMIC EVALUATION

Continue to reassess and improve the business/economic motivation for implementation of a new test based on the biomarker(s):

- Does the test improve patient outcome, reduce costs, shorten/reduce hospitalization, improve selection of treatment, decreases morbidity and mortality?
- Is this achieved without compromising patient outcomes?

Perform a Cost-Benefit Analysis: do the benefits provided outweigh the costs of implementation/administration of the new test.

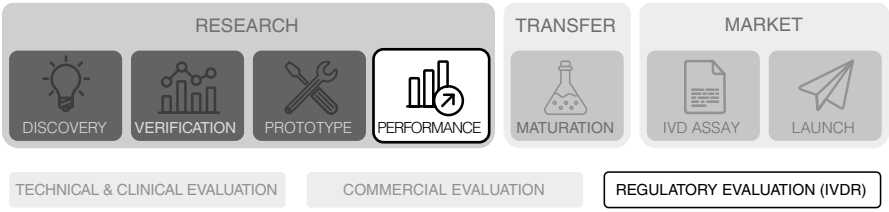
TASK 3. FREEDOM TO OPERATE ANALYSIS

If an FTO has not been performed to date, it must be done now.

Has the target use/application/commercial use scenario changed? If so, consider to update the FTO for the relevant space. Do this jointly with a patent attorney.

AVAILABLE MATERIAL: FREEDOM TO OPERATE (FTO) ANALYSIS

I.4.C. PERFORMANCE: REGULATORY EVALUATION



TASK 1. CHECK IF THE OBTAINED ETHICAL APPROVALS STILL COVER THE NEW STUDIES

Revise the appropriateness and scope of previously obtained ethical approvals. If necessary, obtain new ethical approval and patient consent for your clinical studies release by ethical committee.

TASK RELATED (EXTERNAL) LINKS:

Simon Fraser University – Office of Research Ethics (2017), Consent form guidelines and template.
https://www.sfu.ca/research/sites/default/files/2019-09/2017%2004%2019%20Consent%20Form%20Guidelines%20and%20Template%20DRAFT%20FINAL.pdf

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AVAILABLE MATERIAL: BEST PRACTICES ON PATIENT CONSENTMENT

TASK 2. SUBMIT THE APPLICATION FOR CLINICAL STUDIES

Fulfil requirements for clinical studies of IVD medical devices (Article 57 *General requirements regarding performance studies* & Article 58 *Additional requirements for certain performance studies* of IVDR) and submit the application for clinical studies according to Figure 28 of Regulatory Guide and Article 66 *Application for performance studies* of IVDR. Collect data related to clinical performance of the assay in respect to IVDR requirements. Apply *Annex I Chapter II* (9) *Performance characteristics* of IVDR.

TASK RELATED (EXTERNAL) LINKS:

Simon Fraser University – Office of Research Ethics (2017), Consent form guidelines and template.
https://www.sfu.ca/research/sites/default/files/2019-09/2017%2004%2019%20Consent%20Form%20Guidelines%20and%20Template%20DRAFT%20FINAL.pdf

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 3. COLLECT DATA RELATED TO CLINICAL PERFORMANCE OF THE ASSAY

When the request is approved,

- Start testing by using ISO 20916:2019 standard *In vitro diagnostic medical devices – Clinical performance studies using specimens from human subjects – Good study practices* and
- Familiarize IVDR requirements, apply Annex I Chapter II (9) *Performance characteristics* of 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 the technical documentation provided by the manufacturer.

TASK RELATED (EXTERNAL) LINKS:

Global Harmonization Task Force (2012), Clinical Evidence for IVD medical devices – Key Definitions and Concepts.
http://imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n6-2012-clinical-evidence-ivd-medical-devices-121102.pdf

Global Harmonization Task Force (2012), Clinical Evidence for IVD medical devices – Scientific Validity Determination and Performance Evaluation.
http://imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n7-2012-scientific-validity-determination-evaluation-121102.pdf

Global Harmonization Task Force (2012), Clinical Evidence for IVD Medical Devices – Clinical Performance Studies for In Vitro Diagnostic Medical Devices.
http://imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n8-2012-clinical-performance-studies-ivd-medical-devices-121102.pdf

AVAILABLE MATERIAL: CLINICAL PERFORMANCE CHARACTERISTICS

TASK 4. APPLY FOR UDI CODES OF THE IVD MEDICAL DEVICE

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

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 5. COMPLETE THE DEVICE TECHNICAL DESCRIPTION

- Design device's label and instructions of use – apply Annex I Chapter 3 *Requirements regarding information supplied with the device* of the IVDR.

- Complete the device description which includes device description part/component drawings, assembly drawings and packaging drawings, as well as key components and its operating principles.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 6. GOOD PRACTICES

Perform a preliminary classification of the assay into risk classes according to IVDR guidelines. Apply Article 47 *Classification of devices* and Annex VIII *Classification Rules* of IVDR and follow Figure 36 of the Regulatory Guide. Note:

- IVD biomarker applicable assays typically fall into classes C or D of the four available classes (A, B, C and D).
- Classification into relevant risk class determines the regulatory pathway.
- Preliminary classification could be expected by a business partner.

Asses preliminary general safety & performance requirements according to product characteristics and risks relevant to its use. (Apply Annex I *General safety and performance requirements*, Annex III *Technical documentation on post-market surveillance* of IVDR and Chapter 4.1 of Regulatory Guide.)

From a regulatory standpoint, it is crucial to establish product characteristics and identify risks associated/related to product performance/design as soon as possible. This constitutes a significant input for further technical documentation and is crucial to facilitate collaboration with a potential business partner.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

PHASE ACHIEVEMENTS

First clinical studies completed

Report of clinical performance of the established prototype made

Comparison studies and assessment of accuracy and benefits made

Prepared documentation/technical evidence for technology transfer

Freedom-to-operate search results in place for suggested methodology and components

Report of analytical validity of the established prototype prepared

Assessment of novelty and patentability completed

Decision on final patent “structure” taken

Commercial value propositions, articulated, refined quantified and selected

A Cost Benefit Analysis on implementation of assay vs. cost for the target customer made

Continued refinement of experimentation/documentation practice looking forward to regulatory specifications

SELF-EVALUATION-PERFORMANCE PHASE

CLINICAL NEED

Have you accomplished comprehensive assessment of clinical performance of the established prototype incl. comparison with reference method?	☐ YES	☐ NO
Are aims set for clinical performance characteristics achieved (e.g. AUC, clinical SENS. / SPEC., NPV / PPV)?	☐ YES	☐ NO
Are evidence of health benefits (improved patient outcome) confirmed?	☐ YES	☐ NO

MARKET

Have you performed your economic evaluation and cost effectiveness analysis?	☐ YES	☐ NO
Have you formulated your business case and commercial strategy?	☐ YES	☐ NO
Is positioning in clinical care pathway confirmed (e.g. new step, complementary step, replacement of old test)?	☐ YES	☐ NO
Is cost-effectiveness of test on appropriate level?	☐ YES	☐ NO

FEASIBILITY

Have you secured freedom-to-operate?	☐ YES	☐ NO
Have you estimated the risk class and the regulatory requirements for the assay?	☐ YES	☐ NO

II. TRANSFER STAGE

5. MATURATION PHASE

Pre-industrial maturation phase

TRL-5 Configuration to industrial application (beta prototype)

TRL-6 technology demonstrated in relevant environment

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PHASE DESCRIPTION

Selection of business model (start-up vs. licensing) and initiation of technology transfer.

Accumulation of further clinical evidence by collaboration between academia, industry and/ or end users.

Preparation of preliminary **product*** plan and selection of specific assay chemistry and instrumentation.

Planning for establishing industrial beta-prototype.

Business plan refinement

Self-assessment weighing team strengths, motivation against commercial opportunity considered

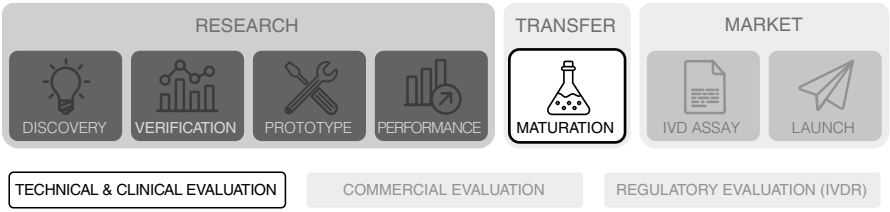
Product plan development for first and later stage product iterations

Considerations of legal aspects pertaining to license agreements, company formation and or partner agreements including: Articles of Association, SHA, licensing

Discussions with regulatory advisors on Quality management systems and standards pertaining to chosen commercial path

***product**: Generally "something that is made to be sold, usually something that is produced by an industrial process or something that is cultivated". In the BIC project the term refers to a physical IVD test (i.e. assay) kit for measuring biomarker(s) or analyte(s) in selected clinical settings (including home and near patient testing).

II.5.A. MATURATION: TECHNICAL AND CLINICAL EVALUATION



TASK 1. BIOLOGICAL CHARACTERISTICS OF THE BIOMARKERS

Continue to expand on and build further knowledge on the biological characteristics of the biomarker(s). If not known or previously documented:

- Where is/are the biomarker(s) produced – e.g. in which organ(s)?
- Is/are the marker(s) intracellular, intra-nuclear and/or excreted?
- What and when triggers biomarker expression and how long is the expression and presence in target tissue/organ/fluid? Is the time window sufficient for testing in routine settings?
- Does it allow detecting the disease at an early stage?
- How many different manifestations (molecular forms) exist and do they change when the disease progresses?
- Are stabilities different in the different forms?
- Can you use the same biomarkers for multiple uses, e.g. first diagnosis and then monitoring the efficiency of treatment?

RELATED TASK

STAGE: Research – **PHASE 1:** Discovery
Technical and Clinical Evaluation

▶

TASK 1
Purpose of the research and study design

STAGE: Research – **PHASE 2:** Verification
Technical and Clinical Evaluation

▶

TASK 1
Biomarkers verification plan

TASK 2. BIOLOGICAL LINK BETWEEN THE BIOMARKER(S) AND THE DISEASE

Investigate the specific association between the biomarker(s) and mechanism of disease, as far as it is not already known.

- What is the specific association and the biological mechanism involved in the disease?
- To which patients does it apply?
- Is/are the biomarker(s) specific to this disease or is there a shared molecular pathology across diseases?
- Is there a reason for the biomarker(s) to be elevated in any benign conditions?

TASK 3. VARIATION AND REFERENCE RANGES BETWEEN SUB-POPULATIONS

- Determine the extent of variation between individuals (e.g. gender, age) and ethnicities belonging to the target population.
- Determine the reference levels in similar healthy populations.
- Determine factors potentially affecting the level of the biomarker in-vivo (e.g. circadian rhythm, food intake) and in-vitro (e.g. stability of the targeted molecular form in different specimen matrixes and in different transport and storage conditions).

Can further contraindications for testing or limitations to the target population be identified?

TASK 4. CROSS-REACTIONS AND INTERFERENCES

- Analyze whether the new assay or any of the specific binders used in it cross-react with biologically related molecules.
- Analyze the effect of relevant endogenous and exogenous interference e.g. by measuring clinical samples known to contain interfering substances such as autoantibodies or certain drugs.
- Report all cross-reactions and assay interferences detected.
- Include any observations made when earlier analyzing specimen cohorts – including healthy individuals. Are there interferences that could be tackled by assay design or chemical additives?
- If not documented previously, what are the clinically relevant concentration ranges for the analyte and the biologically related molecules?

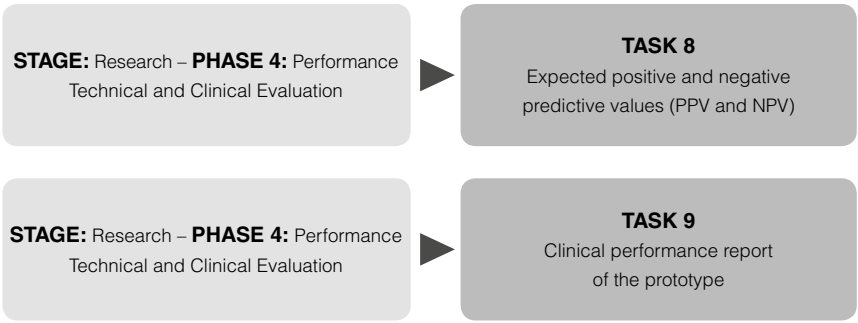
- Is the effect of cross-reactivity diminished or increased by the difference?
- Is there a risk for a high-dose hook effect?

TASK 5. CLINICAL PERFORMANCE CHARACTERISTICS UPDATE

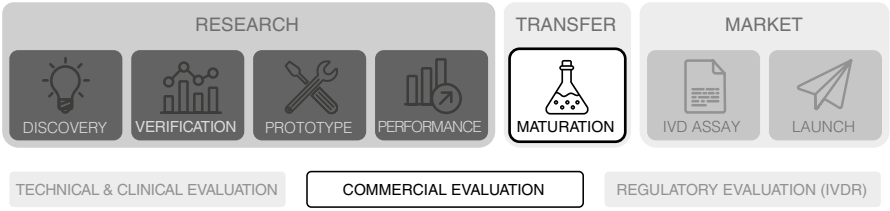
Re-visit the clinical performance characteristics each time a new specimen cohort is analyzed:

- AUC (separately for different stages of disease/time-from-diagnosis where feasible)
- suggested cut-off value
- diagnostic sensitivity
- diagnostic specificity
- negative predictive value (NPV)
- positive predictive value (PPV)
- number of false positives for each one true positive (100/PPV)
- number of false negatives for each one true negative (100/NPV)
- and other applicable measures, e.g. relative risk ratio, hazard ratio, etc.

RELATED TASK



II.5.B. MATURATION: COMMERCIAL EVALUATION



TASK 1. TECHNOLOGY TRANSFER PATHWAY FOR ESTABLISHING A NEW COMPANY

Revisit the options to bring the technology to the market (either via spin-out/company formation/sale or license to a partner). For company formation, a number of general criteria should be met:

- Broad and strong patent protection (e.g. a novel platform, high technical novelty, difficult to copy/reproduce by other means)
- A large and growing market with increased need for the product
- Few competitors or unique value proposition
- Further development is technically feasible
- High potential for extension of product into new conditions/applications
- Strong team with a desire to build a company, including a business- oriented leader (CEO)
- Realistic self-assessment of the time and effort required to build company further
- A solid business plan with a well thought-out go-to-market strategy
- Feasible financing plan

TASK 2. TECHNOLOGY TRANSFER PATHWAY FOR LICENSING OR FULL ASSIGNMENT (SALES OF IPR)

Evaluate alternatives to a spin-out company. Consider licensing to an established company when:

- Narrow patent protection is foreseeable (component or improvement),
- Product fits in an existing commercial product line,
- Expected product development contributions are relatively low,
- Crowded or mature markets with large dominating companies,

TASK 3. CONSIDERATIONS FOR START-UPS/SPIN-OUTS

Perform self- assessment of team and potential company.

QUESTIONS FOR FOUNDERS:

- What qualifications and special professional and personal strengths do the team members possess?
- What is the level of the team's:
  - → commercialization experience and knowledge?
  - → industry experience?
  - → quality management experience?
  - → knowledge of regulatory issues?
  - → knowledge of IPR issues?
  - → entrepreneurial dedication?
  - → What are the weaknesses/ deficits of the team and how can they be compensated?

QUESTIONS ABOUT THE PRODUCT:

- What is special about your offering?
- What is the extent of further Research and Development (R&D) required?
- What kind or premises and instrumentation are required for R&D?
- What kind of premises and instrumentation are required for small-scale production?
- When can zero series production be started?
- How can production be upscaled and when?
- Which quality system requirements need to be fulfilled?
- Which regulatory requirements need to be fulfilled?
- What approvals are required?
- Are there other legal requirements e.g. concerning third party IPR?
- What is the management plan for own IPR?
- What collaboration is required (e.g. all outsourcing required)?
- What are the reimbursement regulations that apply?
- Can reimbursement be obtained? How?

QUESTIONS ABOUT THE CUSTOMERS:

- Who are your customers?
- Where are your customers?
- Do you have reference customers or first assigned customers?

- Is there long-term sales potential associated with the pioneering customers?
- Are you dependent on a few major customers?
- What problems or specific needs do your customers have?

QUESTIONS ABOUT THE COMPETITORS:

- Who are your main competitors?
- Are competitors developing products in a similar direction?
- What is your pricing strategy and why?
- Which calculations form the basis for pricing?
- How competitive is your pricing against the competitors?
- What other advantages dose your product have against competing products?
- Why is your offer better?
- What weaknesses dose your product have compared to competing products?
- How do you compensate for these weaknesses?
- Where are your competitors located and do you have disadvantages due to your own location? How can you compensate for these disadvantages?

QUESTIONS ABOUT SALES AND MARKETING:

- What kind of sales channels and sales partners (distributors) will you use?
- What is the scale of sales pursued?
- What are the geographical areas targeted?
- What is the cost of sales?
- How do your customers find out about your product?
- What marketing measures do you plan to use and when?
- What is the cost of marketing?

QUESTIONS ABOUT OPPORTUNITIES AND RISKS:

- What are the three biggest opportunities that could positively influence the further development of the company?
- What are the three most important problems that could hinder the positive development of the company?

TASK 4. DRAFT BUSINESS PLAN FOR START-UPS

If company formation is feasible and desirable, create/refine the business plan with descriptions/elaborations of:

- Team and competences,
- Market opportunity (need),

- Product (approach/solution),
- Benefits (economical, technical, clinical etc.),
- Competition,
- Financing strategy,
- Product pricing,
- Go-to-market and expansion strategies,
- Timeline and milestones,
- Pre-negotiated terms for acquiring the IPR, if needed from host institution.

TASK 5. DEVELOPMENT PLAN

Establish a detailed plan of the commercial IVD assay development. Include calculations of instrumentation, facilities and resources required and the timeline of each phase. Place special emphasis on the clinical evaluation studies, including who you will collaborate with and what golden standard technology the new product will be compared to.

TASK 6. COST PER CASE EVALUATION

If not done already, expand your Cost-Benefit Analysis to the individual level. Keep in mind that the estimated cost of detecting one person affected (among the population tested) needs to be economically beneficial.

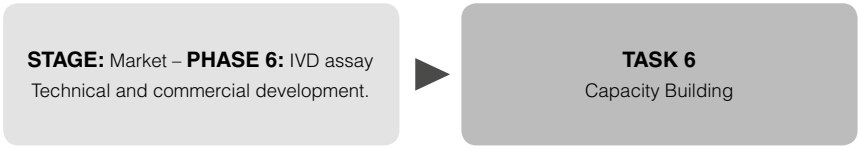
STAGE: Market – **PHASE 6:** IVD assay Technical and commercial development.

TASK 3
Company Internal Pre-project Study for Market Opportunity: Commercial Evaluation

TASK 7. CONNECTIONS WITH INVESTORS

Escalate or initiate discussions with potential investors. Keep in mind:

- Have contact with early stage investors as soon as possible, ideally right after you have an offer for acquiring the IPR.
- Present the business plan and the development plan.
- Expect project valuation feedback with early assessment of the required investment.
- Revise your key documents/development plan according to common feedback received.



TASK 8. STARTING A COMPANY

In conjunction with your TTO/commercial officer, proceed to work on company formation:

- Identify the process of company registration from your national Business Authority
- Identify key registration documents.

If you have not done so previously, have a discussion regarding the Shareholders Agreement (SHA) which reflects expected contributions to the company, remuneration and other key benefits and requirements. Do not postpone this crucial discussion if company formation is the desired path forward.

CONSIDER strongly having a start-up lawyer/mediator present to guide on the technicalities of the legal document as well facilitating the discussion/agreement.

TASK 9. TERMS FOR A LICENSE

Explore the potential/structure of a license agreement. Considerations include:

- Stage of company receiving license (stat-up/early stage v. established/mature)
- Timing and structure of payments i.e. down-payment v. royalties (In some cases, a university/host institution can also participate as a shareholder via an investment-in-kind contribution instead of down-payment).

License term sheets should include:

- Licensor, licensee, date
- Technology description – The exact IPR what is licensed
- Materials transferred
- Territories
- Field(s) of use
- Payment agreement (up-front payments, royalties, annual fees, milestones etc.)
- Ownership of IPR
- Patenting costs (who pays)

- Sub-licensing terms
- Infringement clauses (who acts)
- Duration, diligence etc.

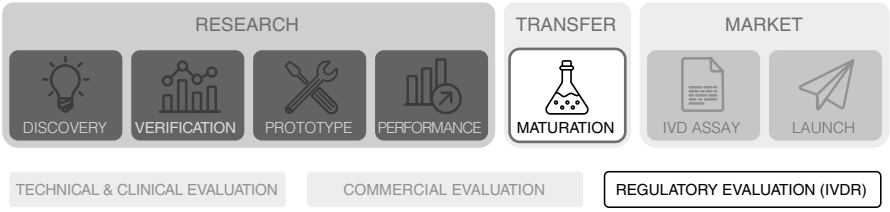
Note that universities in general may encourage spin-outs by offering flexible terms and sharing the market risk in the early years by putting weight on royalties rather than down-payments. Discuss what model suits the business best.

TASK 10. PLAN FOR ESTABLISHING INDUSTRIAL BETA-PROTOTYPE

- Describe the components and preparations (e.g. labelling or other reagent manufacture) required for a beta version prototype.
- Identify features for optimization/removal/addition.
- Establish selection and acceptance criteria for all current/future/desired features.

The above should fit with your **product** roadmap for future versions of the product.

II.5.C. MATURATION: REGULATORY EVALUATION



TASK 1. REVISIT GOOD PRACTICES AS PERTAINING TO REGULATORY ISSUES

The stage concerns technology transfer – no mandatory regulatory requirements to fulfill until SME involvement in the process.

TASK 2. GOOD PRACTICES

- Prepare an overview of the regulatory process/steps from the commercial perspective and of special obligations/requirements e.g. manufacturer obligations.
  - → Apply: Articles 10 to 16 of IVDR – Chapter 4 of Regulatory Guide.
  - → Ideally with a specialist/advisor, begin to consider development/implementation of a formal Quality Management System (QMS) for medical devices, (minimum criteria can be founded in Article 10 (8) *General obligations of manufacturers* of IVDR). Consider the benefits of the system and costs associated since at this time there are no QMS systems available for small enterprises/researchers.
  - → Review and apply ISO 13485. Review and get acquainted with the regulatory affairs guidances.
- Initiate the notified body selection process. It may take up ¾ of a year from first contact to closure of an agreement.
- Develop the roadmap for IVDR implementation, including resource requirements, steering group and distribution of responsibility for the implementation of IVDR. Remember of required registration of authorised representatives and importers according to Article 28 *Registration of manufacturers, authorised representatives and importers*. According to Article 27 (2) *Electronic system for registration of economic operators* Member States may maintain or introduce

national provisions on registrations of distributors of devices which have been made available on their territory.
- Review the supply chain regulations and clarify the roles and responsibilities of business partners (authorized representatives, distributors, importers).
- Conduct regulatory training for any new team members.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

European Union (2020), Overview: Medical devices and In Vitro Diagnostic medical devices (IVDs).
https://ec.europa.eu/health/md_sector/overview_en

European Union (2018), Factsheet for Manufacturers of In-Vitro Diagnostic Medical Devices.
file:///C:/Users/ppbk/Downloads/ivd_mfr_factsheet_v3_en.pdf

CAMD Implementation Taskforce (2018), Medical Devices Regulation/In-vitro Diagnostics Regulation (MDR/IVDR) Roadmap.
https://www.camd-europe.eu/wp-content/uploads/2018/05/NEWS_171107_MDR-IVDR_RoadMap_v1.3-1.pdf

European Union (2020), NANDO (New Approach Notified and Designated Organisations) database.
https://ec.europa.eu/growth/tools-databases/nando/index.cfm

International Organization for Standardization (2016), ISO 13485:2016 – Medical devices – Quality management systems — Requirements for regulatory purposhttps:
//www.iso.org/standard/59752.html

PHASE ACHIEVEMENTS

Thorough understanding of commercial scenarios and impact on required personal commitments, financial benefits

Self Assessment completed: Roles and Motivation for commercial scenarios including spin-out or license

Early stage go-to-market completed, including: defined target customer, pricing, partners, geographic scope, reimbursement (etc.)

Fact base for decision on way forward established: spin-out, license, abandon

Business model selected

Preliminary product characteristics/product plan established

Plan for adapting into a commercial assay platform made

First implementation steps of a Quality Management System taken (who is responsible, what platform, who advises on implementation?)

SELF-EVALUATION-PHASE MATURATION

CLINICAL NEED

have you performed with satisfactory outcome refinement of biological characterization of the biomarker(s)?	☐ YES	☐ NO
have you updated clinical performance indicators along new specimen cohorts?	☐ YES	☐ NO
Do you have further clinical evidence accumulated by collaboration with clinicians / industry?	☐ YES	☐ NO
Have you gathered further knowledge (e.g. link to condition, variation in sub-populations, cross-reactions)?	☐ YES	☐ NO

FEASIBILITY

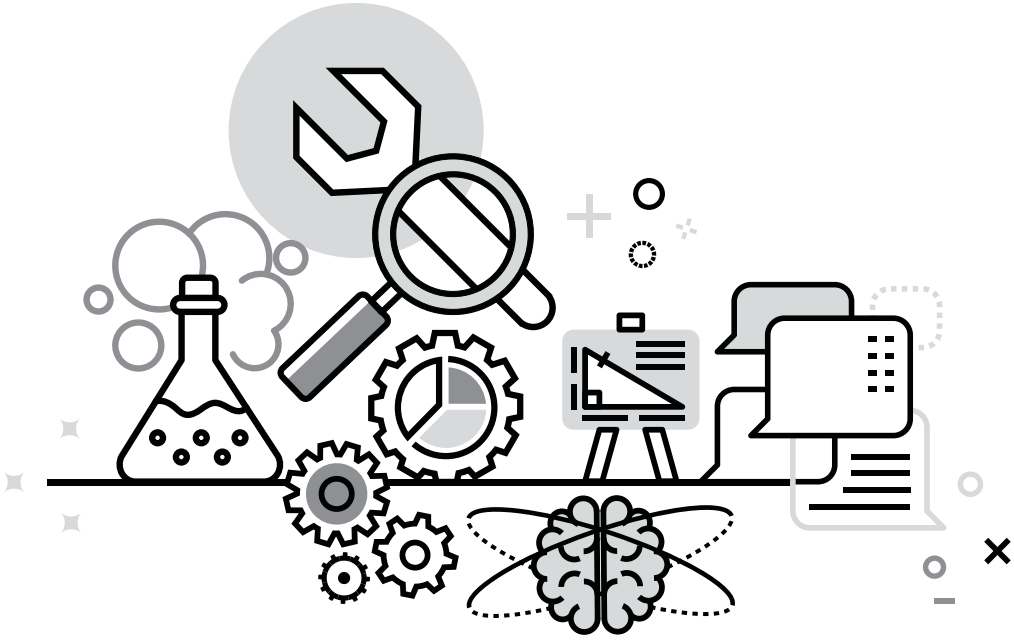
Have you selected your commercialization business model – start-up or licensing/full assignment?	☐ YES	☐ NO
Have you prepared a preliminary product plan and a plan for establishing industrial beta-prototype?	☐ YES	☐ NO
Have you investigated regulatory process from the commercial perspective and especially manufacturer obligations?	☐ YES	☐ NO

III. MARKET STAGE

6. IVD ASSAY PHASE

Industrial assay development

TRL-7 Clinical validation of IVD assay



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PHASE DESCRIPTION

Technology Evaluation and Business
Feasibility Study*

Analytical studies and clinical validation studies performed at multiple evaluation sites

Product concept creation, integration and optimization of components into an industrial prototype in compliance with ISO13485

Transfer-to-production, QMS and building of resources

Preparations for regulatory approvals

***Feasibility study:** an analysis and evaluation of the proposed projects to determine if it (1) is technically feasible, (2) is feasible within the estimated cost, (3) will be profitable. Feasibility studies are typically conducted before companies decide to invest in new product development.

III.6.A. IVD ASSAY: TECHNICAL AND COMMERCIAL DEVELOPMENT

TASK 1. PRODUCT CONCEPT PROPOSAL

Perform feasible commercial estimations based on the points described in the BIC Guide (phases 1-5). Based on this documentation determine whether:

- the biomarker development will be overall advantageous with respect to the existing competing technologies,
- will it dominate a niche,
- or will it be otherwise sensible to commercialize.

THE PRIORITIZATION HAS TO BE EVALUATED FROM COMPANIES' PERSPECTIVE:

1. Proof-of-Principle report completed with assessment of clinical significance
2. Key assay parameters established=>defined (specificity, sensitivity, precision, etc.)
3. Freedom-to-operate search results in place for suggested methodology and components
4. Assessment of novelty and patentability completed
5. Publication plan including patent application strategy drafted
6. Commercial development plan drafted/refined including: estimate of potential market, number of potential users, feedback from potential users and more thorough analysis/understanding of the competitive landscape
7. Early assessment of competition (companies, customers, value drivers) completed, summarized
8. Business model for the new test (e.g. reimbursement strategy and market access strategy)
9. Patent application filed

10. Valid biomarker(s) specific assay prototype established
11. Report of clinical performance of the established prototype made
12. Comparing studies with gold standard methodologies or with comparable commercial IVD assays in the clinical care pathway
13. Listing of key components and optimized assay composition completed (REACH status check)
14. Assay conditions preliminary chosen/optimization performed
15. Preliminary stability tests of components performed
16. First clinical studies completed
17. Comparison studies and assessment of accuracy and benefits made

See BiC guide phases 1-5 and assess availability of scientific research data characterizing parameters of a molecule(s) to be suggested as potential biomarker(s).

See BiC guide phases 1-5 and assess availability of clinical research data characterizing suitability for a proposed molecule(s) to be used in an IVD assay to pinpoint one or several aspects of a disease(s) or condition(s), such as acute infection, result of vaccination, inherent immunity, post-condition effects, etc. Assess availability of technology research data characterizing technology used in the potential IVD assay, mentioned above.

TASK 2. COMPANY INTERNAL PRE-PROJECT STUDY FOR MARKET OPPORTUNITY: TECHNOLOGY EVALUATION AND BUSINESS FEASIBILITY STUDY

The Technological Evaluation and Business Feasibility Study stage is the initial internal SME-performed evaluation stage, and it is based on the previous stages (Stages 1-5) of this BiC guide.

Estimate the suitability of the potential biomarker for company's IVD platform. In other words, you should find out whether the available technology platform could handle the chosen biomarker and assay. As the result of this stage, you should be able to estimate:

- Whether it will be "feasible" to perform the assay using company's Technology Platform, and
- Whether it will generally reflect the Voice of Customer (VOC), marketing needs and the available IPR.

TASK 3. COMPANY INTERNAL PRE-PROJECT STUDY FOR MARKET OPPORTUNITY: COMMERCIAL EVALUATION

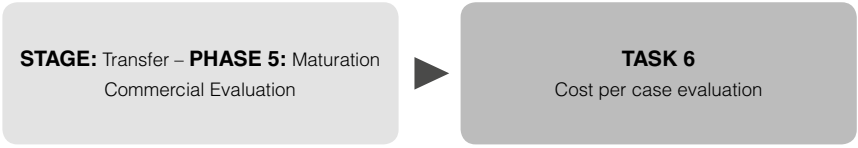
Conduct an evaluation of the market:

- Clinical need and potential market volume
- Preliminary cost feasibility/ profitability assessment
- Competition
- Across different market segments

This evaluation incorporates the demand for a reliable and cost-effective IVD Assay or a Point-Of-Care (POC) test, and the interest of Medical Device distributor(s) to sell and distribute the test to the mass markets.

FREEDOM TO OPERATE ANALYSIS AS PART OF THE COMMERCIAL EVALUATION: Evaluate the entire field of Intellectual Property Rights (IPR), including existing patents, scientific and technical publications, and registered trademarks within the markets under consideration. At this stage, an own IP Portfolio and a separate IP Overview are created, and on their basis an IP Patenting and Publication Plan is designed and written.

RELATED TASK:



TASK 4. PRELIMINARY REIMBURSEMENT EVALUATION AS PART OF THE COMMERCIAL EVALUATION EXPLANATION OF THE TASK AND EXPECTED OUTCOME

Reimbursement mechanisms differ from country to country. It is important to examine the requirements and reimbursement/market access mechanisms. It improves and speeds up the possibilities to have the new test fitting better in the system, which in turn speeds up reimbursement. The trend among European healthcare authorities is to focus on authorizing reimbursement only to the most beneficial medical and medical device products and therefore diagnostic manufacturers are continuously

revising reimbursement and market access strategies to better fit lower-budget-based decision making in Europe. The demand for a proof of a product's scientific and economic value are increasingly challenging for device and diagnostic organizations, with real-world data and Randomized Control Trial -generated evidence requests.

- Successful market penetration will be achieved by starting to plan the market access in key countries well in advance
- It is important to evaluate the settings and environment in which the new biomarker or device will be used
- Evaluation of time schedules and the complexity of reimbursement approval processes is important
- It is important to identify the local decision makers related to new biomarkers and devices and to analyze the suitability of the new product in the reimbursement system as early as possible

HEALTH TECHNOLOGY ASSESSMENT (HTA): In many countries HTA organizations give recommendations that form a basis for reimbursement assessment.

RELATED TASK:

STAGE: Market – **PHASE 7:** Launch Technical and Commercial Development ▶ **TASK 3** Commercial launch: Marketing and Promotion

TASK RELATED (EXTERNAL) LINKS:

Mapping of HTA national organisations, programmes and processes in EU and Norway
https://ec.europa.eu/health/sites/default/files/technology_assessment/docs/2018_mapping_npc_en.pdf

TASK 5. PRELIMINARY MARKETING PLAN

In order to successfully create a preliminary Marketing Plan, the company has to estimate the market needs and wants.

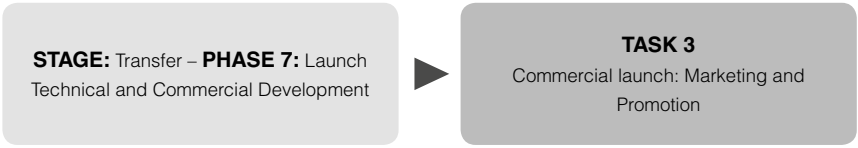
Following needs to be addressed:

- Short summary of market situation;

- Unique selling proposition;
- Preliminary marketing objectives;
- Preliminary analysis of **stakeholders** and customer segmentation;
- Competitor analysis;
- Preliminary assessment of regulatory requirements and documentation;
- Product launch, Distribution and Sales operation plans including pricing and reimbursement assessment.

The actual (or a preliminary) Marketing Plan should be created during the "Project Planning" stage prior to the "Design and Development" and "Product Verification and Validation" stages. The Marketing Plan must be updated to its final form before product launch. The final Marketing Plan can also be included as part of the business plan.

RELATED TASK:



TASK 6. CAPACITY BUILDING

The goal of this stage is to evaluate and identify all resources needed to perform the further stages as efficiently as possible in order to confirm the requirements related to quantity of human resources, equipment, time schedule and funding of further operations.

RESOURCES (TECHNICAL SKILLS, NUMBER OF EMPLOYEES, OUTSOURCING)

Map the quantity and quality of technical skills already available in your company and analyze what kind of technical skills are missing. Also analyze the sufficiency of resources. The missing technical skills can be recruited or the required workload can be outsourced to a collaboration partner.

Resources and skills for regulatory purposes need to be estimated, including a person responsible for regulatory compliance. Outsourcing can also be considered as an option.

Conduct a cost-benefit analysis to evaluate which model fits your company best.

INVESTMENT ANALYSIS

Make a preliminary investment analysis to evaluate financial resources needed. In this analysis, consider at least the following issues:

- acquiring the right kind of premises (including instrumentation) to adjust and control the environment in premises based on product and production requirements,
- investment into production and quality control instrumentation and management,
- evaluation of patenting costs and registration fees. Geographical coverage and technological (including production methods) coverage needs to be assessed,
- other costs to be considered (e.g., samples, surveys, out-sourcing).

PRODUCT DEVELOPMENT COSTS (INCLUDING CLINICAL TRIALS)

Evaluate the amount of investment needed to perform all activities included in the comprehensive development project described above. Investments needed to perform outsourced clinical trials by third parties' laboratories should also be included in a final investment calculation of a development project.

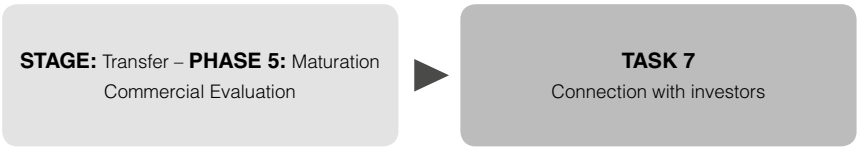
FUNDING AND BUDGETING

Map possible funding sources such as public R&D grants and loans, private investors, business angels, venture capitalists, or crowdfunding on local, national and EU level. Notice that different instruments have different terms, like, for example, company type, required own contribution, age of the company, etc. Capital seekers who can already demonstrate initial success and have a demonstrably functioning and scalable business model are suitable for approaching venture capital (VC) companies. The investment level of venture capital companies starts usually at at least 250 000 euros, depending on the company, but can also be several million euros.

ACCELERATOR AND MENTORING PROGRAMMES

If available, consider applying and participating in local and national accelerator and mentoring programmes.

RELATED TASK:



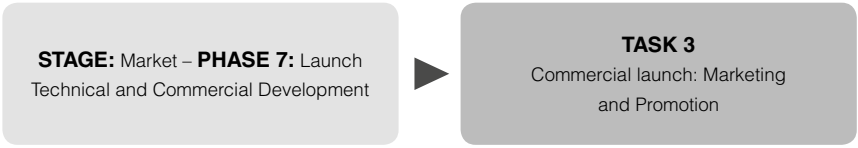
TASK 7. EARLY MARKET VALIDATION

Engage market demand early in the project by:

- Evaluating, consulting and interviewing relevant clinical stakeholders
- Finding and engaging well-known and relevant opinion leader(s)
- Reaching out directly to your potential customers to drum up commercial interest, for example in the form of a letter of intent (LOI) expressing how much they are willing to purchase in test phase and afterwards.
- Spreading awareness of your idea through social media to determine if your value proposition has enough organic interest to build an online following.
- Check the capacity of your distributor network/ start building your distributor network

Performing these early market validation activities will substantially mitigate the business risks of the project. If a project is able to show strong market demand early, it both improves the likelihood of attracting an investment, and it increases the chances of executing a successful go-to-market strategy.

RELATED TASK:



TASK 8. PRODUCT PLANNING AND PRODUCT CONCEPT CREATION

The goal of this stage is to create comprehensive documentation for the project which contains all documentation available from earlier stages 1 – 5 as history files. This stage also puts together all available information and documentation of the product from technological, commercial and regulatory point of view. A project development plan is created including also an initial risk analysis.

CREATE A PROJECT DEVELOPMENT PLAN (OR PROJECT CHARTER): This plan is an "alive" document and should be updated during the entire development process after completion of every stage.

TECHNOLOGY ASPECT OF THE PROJECT CHARTER: A Project Charter document should include all the data collected and created so far:

a. the aim of the project and its scope;
b. the need and demand for the test;
c. solution suggested to satisfy the demand, i.e. de facto application or porting of an assay within the chosen technological platform;
d. justification and feasibility of the proposed solution; and
e. resource allocation.

In addition, a Project Charter must reference external marketing and regulatory documentation, such as the Marketing Plan, Market Needs, Voice of Customer (VOC), User Requirement Specification (URS) and System Requirement Specification (SRS).

COMMERCIAL ASPECT OF THE PROJECT CHARTER: From the commercial and organizational point of view, the Project Charter incorporates:

- product overview;
- project organization;
- resources needed; and
- identifies activities to be performed.

The Project Charter clearly describes the roles and goals of the Project Team. It also refers to Work Breakdown Structure (WBS) and Project Schedule and Gantt chart.

PROJECT TEAM AND THEIR ROLES: The R&D Project Leader and the project team are chosen. The Project Charter is updated and clearly describes the roles and goals of the Project Team.

USER REQUIREMENT SPECIFICATIONS (URS) AND SYSTEM REQUIREMENT SPECIFICATIONS (SRS): Translate "Market Needs and Wants" and the Voice of Customer (VOC) into User Requirement Specifications (URS) or System Requirement Specifications (SRS). URS and SRS include intended use, target customers/users, product and the regulatory requirements. They can further refer to standards recognized by the regulatory authorities of target country for its implementation.

WORK BREAKDOWN STRUCTURE (WBS): The Project Leader creates a WBS. WBS identifies all the tasks of the design and development process separated step-wise in Work Packages (WPs). For every WP, the WBS includes:

- tasks separated into sub-tasks;
- inputs needed from other WPs and sub-projects; and
- the list of deliverables.

This procedure applies to all projects, aiming to develop IVD products under the scope of a Quality Management System (QMS).

DEFINE THE PRODUCT CONCEPT AND SELECT THE ASSAY CHEMISTRY AND INSTRUMENTATION: In this step define the Product Concept, which includes an overall description of the product, components, functions and interface options, accessories, consumables and additional technologies, if required.

INITIAL RISK ANALYSIS: Based on the Product Concept and the preliminary Intellectual Property Rights (IPR) assessments and trademark investigations, described above, the initial Product Risk Analysis is initiated. **Initial Risk Analysis**, such as, for example, the risk of accessibility or unavailability of factors that may delay project objectives and deliverables, is derived from two input factors:

- assumptions on uninterrupted supply and valid certificates; and
- assessment of constraints and limitation that must be taken into consideration prior to the initiation of the project.

CREATE A SCHEDULE: Finally, create a project schedule.

TASK 9. QUALIFICATION OF PRODUCTION FACILITY AND EQUIPMENT (AUDIT BY NOTIFIED BODY)

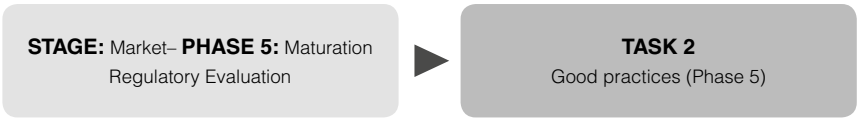
QUALITY MANAGEMENT SYSTEM AND CERTIFICATION OF QMS ISO 13485

The manufacturer must have a quality management system in use (in practice according to ISO 13485). No Notified Body involvement for Class A (excluding sterile devices).

New equipment, processes or facilities must not be taken into use unless a decision about validation requirements and steps needed has been made, and any necessary validations/verifications have been carried out and accepted. Processes are subjected to 100% verification and validation.

Contact your notified body.

RELATED TASK:



STAGE: Market – **PHASE 7:** Launch Regulatory Approvals

TASK 1
Pass through conformity assessment procedure successfully

TASK RELATED (EXTERNAL) LINKS:

European Union (2020), NANDO (New Approach Notified and Designated Organisations) database.
https://ec.europa.eu/growth/tools-databases/nando/index.cfm

International Organization for Standardization (2016), ISO 13485:2016 – Medical devices – Quality management systems — Requirements for regulatory purposes.
https://www.iso.org/standard/59752.html

TASK 10. CREATE DEVELOPMENT PLANS

DESIGN AND PREPARE A PROTOTYPE: Based on the WBS from Stage 2, design and prepare a working prototype of the test. Here, we are not speaking about an assay to be used to detect a particular analyte, but about actual engineering a successful "port" of an assay, for example a sandwich immunoassay to the specific detection platform. As the result, we obtain a working prototype of a test.

CREATE A RISK MANAGEMENT PLAN: "Risk" is a combination of the probability of occurrence of harm and severity of the harm. "Risk Management" is the systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling and monitoring risks. The Risk Management process includes:

- Identification of hazards and potential risks,
- Estimation and evaluation of the risks,
- Controlling these risks, and
- Monitoring the effectiveness of Risk Control throughout the product life cycle.

The scope of the risk management depends on the intended use of the product and its characteristics, as well as the severity of known or foreseeable hazards.

CREATE A REGULATORY PLAN: The Regulatory Plan describes the strategy to meet regulatory compliance with relevant laws, guidelines, etc. The regulatory re-

quirements and the pathway for market clearance on specific markets (as defined in the Marketing Plan) are identified based on the description and intended use of the product. See the regulatory track.

CREATE A PRODUCT VERIFICATION AND VALIDATION PLAN: The Product Verification and Validation Plan includes:

- **Analytical Performance Evaluation plan:** The aim of the analytical performance evaluation is to study and record the analytical performance characteristics of used technological platform and to verify that the design outputs meet the design inputs. The Analytical PE plan usually includes measurement of the following parameters:
  - → *Proof of Precision* to determine the closeness of agreement between independent test results obtained under specified conditions (CLSI guidelines EP05-A3 and EP06-A);
  - → *Detection Capability* to determine what are the Limit-Of-Blank (LOB) and Limit-Of-Detection (LOD) of the test (CLSI guideline EP17-A2);
  - → *Interference* study to determine susceptibility to relevant, possibly interfering endogenous and exogenous substances/agents (CLSI guideline EP07-A2).
- **Clinical Performance Evaluation Plan:** Collection, management and preparation of clinical specimens. Definition of suitable specimen collection devices and sampling methods. Description of specimen processing protocol. Performance evaluation of the specimen processing. Clinical PE must deliver Clinical Specificity, Clinical Sensitivity and the Receiver Operating Characteristic (ROC) analysis.
- **Clinical evidence:** Clinical Performance Evaluation (clinical PE) serves two purposes:
  1. To calculate test parameters of clinical sensitivity, clinical specificity and clinical Positive and Negative Predicted Values (PPV and NPV, respectively); and
  2. Perform the *Equivalence Assessment* of the tested method with respect to the already established and accepted reference method (for example, a Lateral Flow point-of-care SARS-CoV-2 antigen test versus PCR).

Clinical Performance Evaluation is done by the end-user professionals with the statistically relevant number of subjects, with the preliminary determined numbers of "positives" and "negatives" towards the tested value. Then, the numbers of "true positives", "true negatives", "false positives" and "false negatives"

are determined, and the two elements of the clinical PE, mentioned above, are completed. Prior to the clinical PE studies an "informed consent" must be obtained from all study participants and often, but not always, an ethical conclusion from the official Ethical Committee may be required.

- Stability Study Plan: The aim of the Stability Study is to obtain objective evidence about the impact of shelf-life on the Test Kit, and its behavior following transportation.
- Software verification and validation plan: the software verification and validation plan includes:
  1. Summary: Summary includes description of software inputs, outputs and processing function;
  2. Target(s) of validation: The choice of intermediate and final software markers and outputs, used to monitor proper software function, is created;
  3. Reference equipment and materials: Software verification is done using (or referred to) a set of control equipment and materials to obtain predefined result. This may include a reference device, if available, or a Research Use Only (RUO) combination with the specific control hardware and tests.
  4. Test methods and parameters: This point is connected to point #2, but also includes data repetition, memory verifications, export and import checks (between a computer and a smartphone, for example), and also calculating of the error of simulations.
  5. Results and fulfilling of acceptance criteria: Different parameters were used to simulate different results during the measurement: (1) results observed should not show any random value or fluctuating; (2) No lag; (3) Possible error scenarios must be simulated and tested; (4) Correct error messages must be displayed.
  6. Assessment of Deviations: Assessment of deviations, such as longer measurement times, device freeze, deviations arising from human error.
  7. Risk assessment: Based on all the results above, assessment of risks and their probability must be made, and instructions to correct those must be created.

IDENTIFICATION AND APPROVAL OF SUPPLIERS: Supplier Selection is followed by Supplier Approval (Grade A, Grade B or Grade C, based on the following factors: ISO13485 and ISO9001; Questionnaire; Quality Agreement; Supplier History, etc.).

PRELIMINARY MATERIAL SPECIFICATIONS: A template for component-material specification (Arrival inspection, etc.) can be used, if there is no equivalent document available.

TASK 11. PRODUCT VERIFICATION AND VALIDATION

Conduct verification and validation studies as planned in the previous phase and write reports (see the regulatory track BIC Tools 06-09-21 8 / 8 of this phase).

All the Verification and Validation studies are performed and the following reports are written and accepted:

- Performance Evaluation Report (both Analytical and Clinical);
- Stability Study Report;
- Software Verification and Validation Report; and
- Benefit-risk Analysis.

FINALIZING THE DESIGN TRANSFER TO PRODUCTION AND MANUFACTURING

The following Specification Documents and Instructions are written and accepted:

- Final Material Specifications;
- Final Working Instructions;
- Quality agreements for critical suppliers; and
- Labeling and packaging instructions.
- This stage aims to finalize the design transfer to production and manufacturing.

III.6.B. IVD ASSAY: REGULATORY APPROVALS

TASK 1. ADDRESS REQUIREMENT OF EMPLOYMENT OF A PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE (NOT RELEVANT FOR MICRO AND SMALL ENTERPRISES)

Apply Article 15 "Person responsible for regulatory compliance" of IVDR. If it is confirmed that the product is within the scope of IVDR and the biomarker (research result) is already considered as a product, it is a good time to recruit a person responsible for regulatory compliance, who possesses the requisite expertise in the field of IVD medical devices.

RELATED TASK:

STAGE: Market – **PHASE 7:** Launch
Technical and Commercial Development

▶

TASK 1
CE Marking and registration of the product

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

Medical Device Coordination Group (2019), Guidance on Article 15 of the Medical Device Regulation (MDR) and in vitro Diagnostic Device Regulation (IVDR) regarding a "person responsible for regulatory compliance" (PRRC).
file:///C:/Users/ppbk/Downloads/Guidance%20on%20Article%2015%20MDR-IVDR%20%20Person%20responsible%20for%20Regulatory%20Compliance.pdf

TASK 2. DETERMINE REGULATORY PATHWAY OF THE PRODUCT

EXPLANATION OF THE TASK AND EXPECTED OUTCOME

- Apply Article 48 *Conformity assessment procedures* of IVDR and follow Figure 37 of the Regulatory Guide.
- Note that the regulatory pathway depends on risk class and intended use of the product.
- Continue to monitor progress of the IVDR implementation plan.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 3. PLAN DEVELOPMENT OF PRODUCT'S TECHNICAL DOCUMENTATION

Apply chapter 4.2 and 4.3 of the Regulatory Guide.

TASK 4. REQUIREMENT OF PROVIDING SUFFICIENT FINANCIAL COVERAGE IN RESPECT OF POTENTIAL LIABILITY REGARDING DAMAGES CAUSED BY DEFECTIVE DEVICE

Apply Article 10 (No. 15) *General obligations of manufacturers* of IVDR.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 5. FINAL CLASSIFICATION OF THE BIOMARKER PRODUCT INTO IVD RISK CLASS AND VERIFICATION OF GENERAL SAFETY & PERFORMANCE REQUIREMENTS

- Apply Article 47 *Classification of devices*, Annex I *General safety and performance requirements* and Annex VIII *Classification rules* of IVDR and Sections 4.1 and 4.4.1 of the Regulatory Guide.
- The project team/company (if established) is responsible for the final classification of the product into risk classes (A, B, C, D) The classification should be conducted on the basis of product characteristics and risks related to its use. The team/company is able to carry out the classification internally driven primarily by team/company researchers. However, where uncertainty exists, seek the advice of a notified body or national authority.
- Familiarize/plan for the IVDR requirements regarding the GSPR.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 6. VERIFY USEFULNESS OF THE DATA & RESULTS FROM RESEARCH PHASES

- Check the completeness and quality of the data.
- Verify that the data meets the critical criteria and determined research methods.

- Verify which data & results you can use for purpose of the development of technical documentation.

TASK 7. FULFILMENT OF GENERAL SAFETY & PERFORMANCE REQUIREMENTS

Apply Annex II *Technical documentation* No. 4 *General safety and performance requirements* of IVDR.

Compliance or non-compliance with GSPR standards has to be documented. When a standard is not relevant for a product, an explanation must be provided why the standard does not apply. Currently standards under the link below 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 norms: ISO, GHTF/IMDRF, FDA and CLSI standards). Task related (external) links:

European Union (2020), Commission Implementing Decision (EU) 2020/439 of 24 March 2020 on the harmonised standards for in vitro diagnostic medical devices drafted in support of Directive 98/79/EC.
https://eur-lex.europa.eu/eli/dec_impl/2020/439/oj

TASK 8. DEVELOP TECHNICAL DOCUMENTATION CONCERNING PRODUCT VERIFICATION & VALIDATION

APPLY:

- Annex II *Technical documentation* No. 6 *Product verification and validation* of IVDR.
- Chapter 4.2.2 of Regulatory Guide.

Continue working on technical documentation for product verification & validation, integrating new research results when relevant. Well documented material benefits:

- Verification & validation: a pre-requisite for registration and placing product on the market.
- Once done, the section serves as the basis for further regulatory documentation requirements.
- Note that, the product verification & validation requires performance studies to be conducted with ethical approval and a submitted application is obligatory.
- Apply ISO 20916 for clinical performance studies.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 9. DEVELOP FULL TECHNICAL DOCUMENTATION UNTIL IT IS SUFFICIENT TO PASS THE CONFORMITY ASSESSMENT PROCEDURE

APPLY:

- Annex II *Technical documentation* and Annex III *Technical documentation on post-market surveillance* of IVDR.
- Chapter 4.2 and 4.3 of the Regulatory Guide.

Initiate development of the six main parts of product documentation, according to IVDR requirements, including e.g. kit inserts, instruction manuals, labels, descriptions of the device and its parts etc., as well as technical documentation on post-market surveillance (PMS plan).

Develop technical documentation in the most practical way, until it is complete and appropriate for the relevant conformity assessment procedure.

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

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 10. GOOD PRACTICES (PHASE 6)

Check the availability/capacity of the notified body before submission of the application.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

PHASE ACHIEVEMENTS

- Quality management system in use
- IVD risk class of the product defined
- Preliminary marketing plan prepared
- Product concept created
- Verification and validation studies performed
- Person responsible for regulatory compliance designated
- Conformity assessment procedure performed

SELF-EVALUATION-IVD ASSAY PHASE

CLINICAL NEED

Have you estimated the scientific and technological suitability of the potential biomarker to your platform?	☐ YES	☐ NO

MARKET

Have you evaluated the market potential of the product?	☐ YES	☐ NO
Have you estimated resources: staffing and budget?	☐ YES	☐ NO

FEASIBILITY

Have you created a project development plan?	☐ YES	☐ NO
Have you contacted your notified body?	☐ YES	☐ NO

III. MARKET STAGE

7. LAUNCH PHASE

Commercial launch and clinical implementation

TRL-8 Commercial launch of IVD assay

TRL-9 Post launch monitoring of IVD assay

GO TO TABLE OF CONTENTS

PHASE DESCRIPTION

CE marking, Certificate of free sale, EU declaration of conformity, Product notification to authority

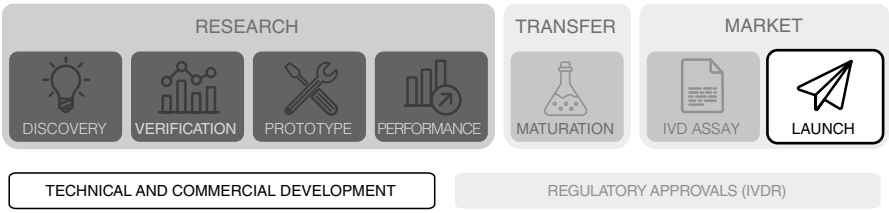
Marketing plan and distributors

Commercial launch of the product

Introduction of the product into the clinical care pathway

Post market surveillance plan

III.7.A. LAUNCH: TECHNICAL AND COMMERCIAL DEVELOPMENT



TASK 1. CE MARKING AND REGISTRATION OF THE PRODUCT

The purpose of the Launch stage is to complete the information necessary for the product registration and obtain CE Marking (see also the regulatory track). The person responsible for regulatory compliance (PRRC), often the Quality and Regulatory Affairs Manager, shall ensure that the technical documentation and European Union (EU) declaration of conformity are prepared and kept up-to-date. The product is manufactured following the final specifications and working instructions, and processes are controlled. The agreement with importers and distributors shall include provisions for the IVDR.

TECHNICAL DOCUMENTATION AND THE EUROPEAN UNION (EU) DECLARATION OF CONFORMITY

The quality and regulatory affairs manager (the QC Manager) shall ensure that the technical documentation and the European Union (EU) Declaration of Conformity are prepared and kept up to date. The product is manufactured following the Final Material Specifications and Working Instructions, and all the processes are controlled. Each product undergoes a product Audit, which ensures the following:

- preparation of the technical documentation before placing a product on the market;
- guarantee that the technical documentation is made available to the market surveillance authorities as soon as the product is placed on the market; and
- keeping the technical documentation for 10 years from the date the product is placed on the market.

The technical documentation is necessary to prove the product meets the essential requirements and therefore justify and support an EU **Declaration of Conformity**. One needs the documentation above to affix the CE marking.

RELATED TASKS:

STAGE: Market – **PHASE 6:** IVD assay Regulatory approvals

TASK 1
Address requirement of employment of a person responsible for regulatory compliance (not relevant for micro and small enterprises)

STAGE: Market – **PHASE 7:** Launch Regulatory approvals

TASK 1
Pass through conformity assessment procedure successfully

TASK RELATED (EXTERNAL) LINKS:

CE Marking – obtaining the certificate, EU requirements
https://europa.eu/youreurope/business/product-requirements/labels-markings/ce-marking/index_en.htm

AVAILABLE MATERIAL: GUIDANCE ON ARTICLE 15 MDR IVDR PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE

AVAILABLE MATERIAL: FACTSHEET FOR AUTHORISED REPRESENTATIVES, IMPORTERS AND DISTRIBUTORS OF IVD MEDICAL DEVICES

TASK 2. LABELLING OF THE PRODUCT

Ensure proper labelling of the product. Labelling should include: instructions for use including intended use, warnings, contraindications, Unique Device Identifier (UDI), etc.

GENERAL INFORMATION:

Registration in EUDAMED (European Database on Medical Devices) and application of UDI (Unique Device Identification) and BUDI (Basic Unique Device

Identification) identifiers concern ONLY manufacturers, which include device manufacturers, test manufacturers, component manufacturers, etc. Registration in EUDAMED is free. Registration timeline is as follows:

- Timeline for placing UDI-carriers on the labels of devices (IVDR Article 113(3)(e), Article 24(4)):
- For class D (highest risk) devices (such as COVID IVD test kits) applies from 26 May 2023 onward;
- For class B and class C devices applies from 26 May 2025 onward;
- For class A (low risk) devices (such as measurement IVD instruments, etc.) applies from 26 May 2027 onward.

USE OF UDI:

UDI is a standardized identification system of all medical devices including every packaging configuration and packing level, excluding shipping containers.

- Basic UDI-DI is the access key for device-related information entered in EUDAMED;
- Reference to Basic UDI-DI must be present in all key documentation (Declaration of conformity, certificates);
- UDI shall be used for reporting serious incidents and field safety corrective actions.

OBTAINING UDI:

Current UDI Issuing Entities are:

- Informationsstelle für Arzneispezialitäten (IFA GmbH),
- GS1 AISBL ("GS1 Finland" for Finland, for example),
- Health Industry Business Communications Council (HIBCC), and
- International Council for Commonality in Blood Banking Automation (ICCBBA).

PROCEDURE:

1. Obtain UDI;
2. Register UDI in EUDAMED.

TASK RELATED (EXTERNAL) LINKS:

Review product labelling, see Annex I Chapter III: European Union (2017), IVD Regulation 2017/746
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

AVAILABLE MATERIAL: UDI SYSTEM UNDER THE EU REGULATIONS 2017/745 AND 2017/746

AVAILABLE MATERIAL: BUDI AND UDI ATTRIBUTES

TASK RELATED (EXTERNAL) LINKS:

EUDAMED UDI USER GUIDE
https://www.medical-device-regulation.eu/eudamed-documents/

TASK 3. COMMERCIAL LAUNCH: MARKETING AND PROMOTION

Initiate marketing and promotion activities early in the process.

FINALIZE THE MARKETING PLAN AND MARKETING MATERIALS

- Finalize the marketing plan that you started developing in phase 6 (Preliminary Marketing Plan).
- Set your budget. Example marketing expenses include outsourcing costs to a marketing agency and/or other providers, marketing software, paid promotions, events (those you'll host and/or attend).
- Build your marketing plan around your competitive advantage. Conduct a SWOT analysis: what are your Strengths, Weaknesses, Opportunities, and Threats?
- Find the right customers with the STP Model (Segmentation, Targeting and Positioning) and don't forget about the 7Ps of Marketing: Product, Price, Place, Promotion, People, Process and Physical Evidence. Use the 7P Formula to continually evaluate and re-evaluate your business activities.
- Your marketing plan should include SMART goals: Specific, Measurable, Attainable, Relevant, and Time-bound. In other words, all your goals should be specific and include a time frame for which you want to complete it.
- Prepare your tactics on how to reach the goals, define your marketing channels and set your action items.

- Businesses with extensive social media presence might consider developing a separate social media plan.

INTRODUCE THE ASSAY INTO THE CLINICAL CARE PATHWAY

- Contact and convince key opinion leaders, end-users (hospitals, clinicians), buyers and payers about your product. Collect and present your data on key advantages, clinical utility, novelty, cost/ benefit, reimbursement.
- Be visible at meetings and appropriate conferences.

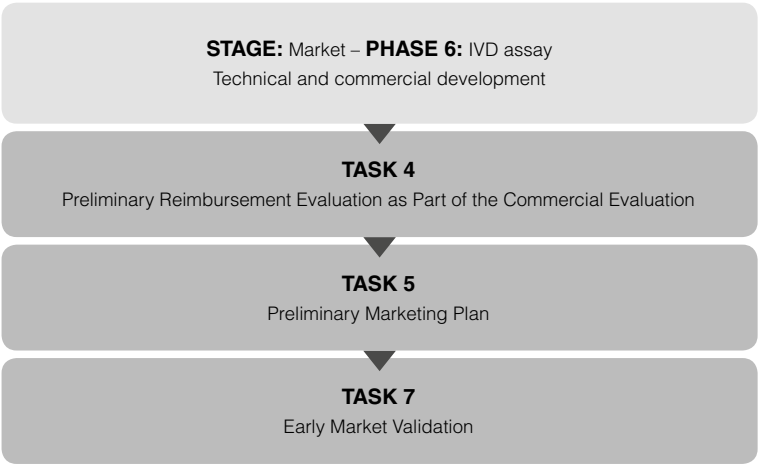
FIND AND SELECT DISTRIBUTORS

- Decide which intermediaries will be involved in the distribution chain and also think about the logistics behind getting the product to the end customer, including storage and transportation.

DETERMINE YOUR PRICING AND REIMBURSEMENT STRATEGIES

- When deciding on pricing, you shoud also consider local reimbursement mechanisms in different countries in collaboration with your distributors.

RELATED TASKS:



TASK RELATED (EXTERNAL) LINKS:

Finding The Right Customers With The STP Model
https://blog.oxfordcollegeofmarketing.com/2020/06/24/finding-the-right-customers-with-stp-model/

Read more about the 7P Formula
https://blog.oxfordcollegeofmarketing.com/2020/10/08/understanding-the-7ps-of-the-marketing-mix/

TASK 4. AGREEMENTS WITH IMPORTERS AND DISTRIBUTORS

Make agreements with importers and distributors to make sure that you comply with the import and export regulations of the country where your IVDR or Point of Care device is being used.

The agreement with importers and distributors shall include provisions for the IVDR (currently, IVDR 2017/746), described in articles 13 (*General obligations of importers*) and 14 (*General obligations of distributors*), respectively. Importers shall place on the Union market only devices that are in conformity with the IVDR. Distributors shall, in the context of their activities, act with due care in relation to the requirements of the IVDR.

AVAILABLE MATERIAL: FACTSHEET FOR AUTHORISED REPRESENTATIVES, IMPORTERS AND DISTRIBUTORS OF IVD MEDICAL DEVICES

TASK 5. POST PRODUCTION

Perform a post-market surveillance plan, report corrective actions and finally conduct a product review post-production.

POST-MARKET SURVEILLANCE PLAN & REPORT: produce a post-market surveillance plan to collect systematically and actively information to update the technical documentation. As defined in IVDR (currently, 2017/746), the post-market surveillance includes "all activities ... for the purpose of identifying any need to… apply any

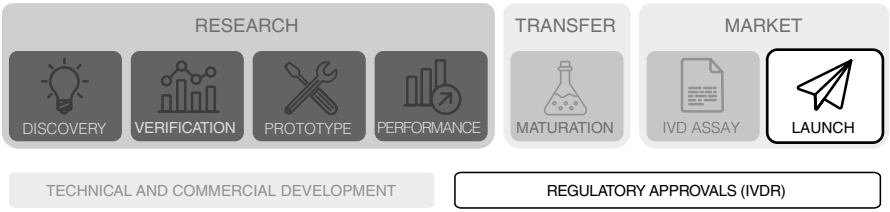
necessary corrective or preventive actions". The information (e.g. customer feedback, non-conformance handling), generated during the production, is the input for product maintenance and improvement. Product documentation must be updated if any changes to the product are applied.

CORRECTIVE ACTIONS: The production manager, product manager or equivalent shall gather data to update the product information on risk management, design and manufacturing information, Instructions for Use (IFU) and labeling, performance evaluation, identification of needs for preventive, corrective or field safety corrective actions etc. The gathered data is input for Product Review: This review should be conducted within 6-12 months after product launch and is intended to confirm that the final output of the project meets the defined objectives. Corrective actions for the product are implemented as according to the "corrective and preventive actions" procedure.

PRODUCT REVIEW: This stage is closed by the completion of the Product Review, which includes documentation on the post-market surveillance report.

POST-MARKET SURVEILLANCE REPORT(PMS REPORT): Manufacturers of class A and B devices shall prepare a post-market surveillance report summarising the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Article 79 together with a rationale and description of any preventive and corrective actions taken. The report shall be updated when necessary and made available to the notified Periodic safety update report (PSUR): Manufacturers of class C and class D devices shall prepare a periodic safety update report ('PSUR') for each device and where relevant for each category or group of devices summarising the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Article 79 together with a rationale and description of any preventive and corrective actions taken.

III.7.B. LAUNCH: REGULATORY APPROVALS



TASK 1. PASS THROUGH CONFORMITY ASSESSMENT PROCEDURE SUCCESSFULLY

Conformity assessment procedures differ in complexity and scope. Follow the prior determined regulatory pathway relevant to the product risk class.

- Choose the notified body from the NANDO system and submit application for conformity assessment.
- Cooperate with the notified body in order to pass the procedure.

RELATED TASKS:

STAGE: Market – **PHASE 7:** Launch
Technical and commercial development

▶

TASK 1
CE Marking and registration of the product

STAGE: Market – **PHASE 6:** IVD assay
Technical and commercial development

▶

TASK 9
Qualification of Production Facility and Equipment

TASK RELATED (EXTERNAL) LINKS:

European Union (2020), NANDO (New Approach Notified and Designated Organisations) database.
https://ec.europa.eu/growth/tools-databases/nando/index.cfm

TASK 2. ADDRESS THE ADDITIONAL REQUIREMENTS BEFORE PRODUCT IS PLACED ON THE MARKET: AFFIX CE MARK, DRAW UP UE DECLARATION OF CONFORMITY, SUBMIT PRODUCT NOTIFICATION TO COMPETENT AUTHORITY, DRAW UP THE CERTIFICATE OF FREE SALE

- Affix CE mark according to Article 18 *CE marking of conformity* and Annex V *CE marking of conformity* of the IVDR.
- Draw up EU declaration of conformity according to Article 17 *EU declaration of conformity* and Annex IV *EU declaration of conformity* of the IVDR.
- Draw up notification to competent authority (template provided by authority website).
- Draw up the certificate of free sale according to Article 55 *Certificate of free sale* (template provided by authority website).

GOOD PRACTICES TO KEEP IN MIND

- Check validity of templates.
- The declaration of conformity shall contain all the information required for identification of the European Union legislation to which the declaration relates, therefore, if there are some aspects not covered by IVDR the manufacturer must still draft up single declaration (details as in description).
- Monitoring of expiration dates of conformity certificates.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 3. COMPLETE THE IVD MEDICAL DEVICE REGISTRATION

Apply Article 26 *Registration of devices*, Article 28 *Registration of manufacturers, authorised representatives and importers* and Chapter 4.2.1 of the Regulatory Guide through the registration procedure within the EUDAMED database.

TASK 4. FULFILL OBLIGATIONS REGARDING POST MARKET SURVEILLANCE SYSTEM AND VIGILANCE REQUIREMENTS – CONTINUOUS PROCESS THROUGH ENTIRE PRODUCT LIFECYCLE

APPLY:

- Articles 80-84 of IVDR
- Chapters 3.7 and 4.3 of the Regulatory Guide

Fulfill the following obligations when the product is already on the market:

- Report any serious incident and any field safety corrective actions (in accordance with Article 82 (1) *Reporting of serious incidents and field safety corrective actions* and Article 84 (5) *Analysis of serious incidents and field safety corrective actions* of the IVDR, and also in form of periodic summary reports (Article 82 (9) *Reporting of serious incidents and field safety corrective actions* of the IVDR).
- Trend reporting (in accordance with Article 83 *Trend reporting* of the IVDR)
- Reporting on safety (Article 80 *Post-market surveillance report* and Article 81 *Periodic safety update report* of the IVDR).

Analysis of serious incidents and field safety corrective actions a.o. prepare safety notices (in accordance with Article 84 (8) *Analysis of serious incidents and field safety corrective actions* of the IVDR).

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 5. COOPERATE WITH NATIONAL ENTITIES TO ENSURE SAFETY (MARKET SURVEILLANCE REQUIREMENTS) – CONTINUOUS PROCESS SUPERVISED BY COMPETENT AUTHORITIES.

- Prepare for additional requirements/reviews after the product is placed on the market:

- Anticipate for checks on the conformity, characteristics and performance of devices including, where appropriate, a review of documentation and physical or laboratory checks on the basis of adequate samples.
- Prepare to take all appropriate and duly justified corrective action to bring the device into compliance with the requirements of IVDR.
- Potentially restrict the making availability of the device on the market, modify the product to specific requirements or to withdraw the device from the market, or to recall it, within a reasonable period that is clearly defined and communicated to the relevant economic operator.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

TASK 6. GOOD PRACTICES (PHASE 7)

- Continue to actively monitor the regulatory environment for amendments, new requirements.
- Track the European Commission website for any potential amendments on IVDR.

TASK RELATED (EXTERNAL) LINKS:

European Union (2017), IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX-:32017R0746

European Union (2020), Overview: Medical devices and In Vitro Diagnostic medical devices (IVDs).
https://ec.europa.eu/health/md_sector/overview_en

PHASE ACHIEVEMENTS

CE marking obtained and product registered in Eudamed (Eudamed launched in May 26, 2022)

Marketing plan and materials finalized

Agreements with distributors made

Product launched on market

Post market surveillance planned and ongoing

SELF-EVALUATION-LAUNCH PHASE

MARKET

Have you finalized your marketing plan?	☐ YES	☐ NO
Have you set up new or your existing distribution channels?	☐ YES	☐ NO

FEASIBILITY

Have you registered to EUDAMED database?	☐ YES	☐ NO
Have you applied for CE-mark?	☐ YES	☐ NO
Have you prepared your post-market surveillance plan?	☐ YES	☐ NO

IV. AVAILABLE MATERIAL

Tips and Good practices

GO TO TABLE OF CONTENTS

BEST PRACTICES ON PATIENT CONSENTMENT

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

When designing a new clinical study, the wording in the voluntary informed consent that the patients (or their legal representatives) sign should be formulated carefully as it dictates the future use of the specimens.

BEST PRACTICES:

- Follow the format as suggested by the local ethics committee (each of which committees act in accordance with the Declaration of Helsinki for ethical principles for medical research involving human subjects), but also prepare for continuing research and utilization of the results obtained.
- Try to describe the scope and field of research at a level that is not too heavily bound on the ongoing project but rather allows use of the collected specimens in future projects involving other analysis techniques and/or targeting other molecules. The duration of storage of the specimens should be long enough to allow such continuing research.
- Also incorporate that the results obtained by using the specimens may be used for commercial purposes with the aim of producing new and more effective diagnostics and drugs for the diseases being investigated.
- Describe the anonymization process in the case that specimens are transferred between organizations. In the patient consent, include right for such transfer.
- Consult your legal department on which requirements of the EU General Data Protection Regulation (GDPR) need to be taken into account in your case.

BEST PRACTICES ON THE DEFINITION OF THE CLINICAL NEED, CLINICAL UTILITY AND CLINICAL BENEFIT

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

CLINICAL NEED

The most important requirement for a new biomarker IVD test is being able to answer a clear unmet clinical need. The need must origin from (or be confirmed by)

the end users and be of type "must have", not "nice to have", because few paying customers exist for the latter kind. Wider acceptance and successful commercialization of a new biomarker test can only be gained if it fills a proven and topical need of the end users. (Also see the chapter on social, psychological, ethical and legal impacts of testing.).

BEST PRACTICES:

- **ESTABLISH A CLEAR INTENDED PURPOSE FOR THE TEST.** A new biomarker test must provide an answer to an unmet clinical need which is correctly understood and confirmed by the real-life end users.
- **ENTER EARLY IN A DIALOG WITH CLINICIANS** (or other relevant opinion leaders or end users). Establishing the clinical need is a natural part of a non-commercial research project when the researchers are medical doctors or have other competences such as contacts to clinicians that allow them to verify the clinical relevance of the biomarkers. Otherwise dialog with relevant clinicians, preferably key opinion leaders, needs to be started as early as possible. Literature studies can only partially be employed to establish the clinical need. The feedback from the end users (or relevant industry in the field when they are the end users) needs to be documented.
- **LEARN FROM THE ABOVE DISCUSSIONS.** Listen to the opinions and potential critique of the potential customers. This will help in understanding the limitations of the technology and making better practical use of the research while turning it into something that benefits the society the most.

PITFALL PRACTICES:

- Looking for a problem to fit one's solution (rather than answering an existing, significant clinical question or need).
- Not listening to the potential customers. The need must origin from real-life end users.
- Bad market analysis: there is a need but also alternative testing methods that perform well.

CLINICAL UTILITY AND CLINICAL BENEFIT

Clinical utility means the ability of an IVD test to positively influence the clinical outcome when introduced in the clinical care pathway (synonyms: clinical pathway, care pathway, care model, care map, care process). The European IVD Regulation (IVDR, 2017/746) also uses the term "clinical benefit" in the context of an IVD

device having a "positive impact related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health". Only biomarkers that provide clear clinical benefits are amenable to translation into clinical use.

BEST PRACTICES:

- A new biomarker test must add benefit for patients and society as compared to the existing clinical care pathway. Also the harms related to testing need to be considered, as well as populations in which testing is not justified.
- A new biomarker test must also concretely help clinicians at their work. A biomarker test must provide information that reflects the current or future situation of the patient without hindsight. The test needs to give a clear answer to a clear clinical question, for example by providing a more accurate or timely diagnosis of a disease or allowing to choose the most efficient therapy for the patient belonging to the target population.
- A new IVD test needs to be directly compatible with the clinical assessment of the patient.
- There must be a proven link between the biochemical pathway of the disease and the biomarker used for its indication.
- The expression of the biomarker needs to be specific for the indication investigated. Understanding the mechanism of disease/therapeutic effect is important.
- Patent protection of a new biomarker should be started only when a clear clinical indication and sufficient scientific evidence has been generated.
- The key criteria for a high-impact IVD-applicable biomarker include, e.g. the biomarker:
  - → addresses a significant unmet medical need (or replaces an unsatisfying existing solution) with a potentially considerable impact on public health,
  - → has specific association with the disease in the target population or allows separating patients benefiting from treatment/non-treatment (i.e., aids in medical decision making),
  - → provides information that is not readily available by clinical assessment,
  - → determination of the biomarker will result in significant improvement in the approval or delivery of care to patients, i.e., facilitates therapeutic decisions with low risk of under- or over diagnostics,
  - → is present in sufficiently high levels to be measured by practical assays,

→ is present in the clinical specimen for a sufficiently long time window; uses a non-invasive specimen matrix,
→ is indicative of the present or future status of the patient,
→ has a high potential market size and value as the driving force for commercialization,
→ convinces clinicians and does not involve unnecessarily complex result interpretation.

BEST PRACTICES:

- Conclusions are drawn too early. Conclusions on the clinical utility are drawn based on the first observations (presence or concentration is different in the affected and healthy persons at group level or between paired specimens).
- The use of the new marker requires complex setups. The need to use complex, personalized decision trees containing multiple different markers (or even multiple molecular types of markers) in varying combinations can limit the clinical utility of new tests. When developing sequential multi-parameter testing processes, the correct use must be clear and transparent for the clinician.

TIPS FOR WRITING A GOOD LAB BOOK

Keep track of any lab activity in the lab book. Take time to update the lab book, preferable after each activity. Do not postpone updating your lab book.

Remember: It is an official document!

Consider digital lab book, but have a notepad close to you all the time. In general, when possible and manageable follow the rules and guidelines of Good Laboratory Practices/Good Scientific Practice/ Good Documentation Practice. These practices will help you keep your lab books in the most optimal way to ensure reproducible experiments as well as provide

HIGHLIGHTS:

- Organize the page layout preferably using the same template. It saves time.
  → Your name,
  → Page number,
  → Experiment number.

- Create from the beginning a suitable experiment numbering system, where related experiments can be sorted and linked.
- Create a numbering system for reagents produced by your experiments, so all experimental products have an unique ID.
- Purpose of the experiment,
- Experiment setup preferable with illustrations/pictures.
- Reagents ID and quantities used,
- Write actual temperature conditions (instead of just "room temperature") both for storage of samples and incubation.
- Write actual pH values, incubation time etc.
- Equipment ID and settings,
- Document all results and observations:
  - → Note any specific or unusual observations during the experiment. Take time to write more detailed than you think you need.
  - → Insert printed photos of the setup and results.
  - → Date and sign the page after each experiment/workday.

TIPS FOR A GOOD DECLARATION OF INVENTION

1. DESCRIBE THE BACKGROUND FOR THE INVENTION

Describe your context of development, what are the specific challenges you faced and that you have tried to overcome by making this invention.

2. COMPETITIVE ADVANTAGE & CLINICAL NEED

Describe thoroughly the current technical solution used for solving the issue? What is the current procedure, the golden standard?

What is the clinical context in which you will apply your invention? Can you think of other areas?

Why is your invention smarter than the previous/current solutions? Which add value do you bring? On which criteria? (Sensitivity/specificity?, Less invasiveness for patients? Better economic approach?)

Is your invention most applicable to a specific subgroup of patients?

3. COMPETITORS AND MARKET

Who are the main company you will think of either as potential partner or competitor? Why?

Could you provide relevant references/literature for the TTO to use when studying your invention?

4. FUTURE PRODUCT

What is your vision for implementation of this invention? How do you imagine it as the ideal final product?

What are you able to develop further by your own? How. Which complementary expertise would you like to have access to? To what purpose and when?

BEST PRACTICES ON CLINICAL SPECIMENS

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

The means for ensuring a high quality of specimens used in biomarker studies should be included in the project plan and be an essential part of risk management of the project. Specimen integrity is one of the factors of highest importance when making conclusions from the clinical performance analyses.

Pairing or matching case and control specimens is often performed at the discovery stage because the disease prevalence is often low, because random selection could result in imbalance of some factors varying between individuals and specimens, and because the throughput of the discovery analysis methods is typically low. The extent of specimen picking needs to be gradually decreased when the research proceeds.

BEST PRACTICES:

- Prepare a specimen management plan spanning e.g. the sampling, handling, stability, preservatives, storage, shipping, de-identification, chain-of-custody (an action audit trail that contains information when the specimens have been used, by whom, for what purpose etc.), patient consent, ethical approval, restrictions-for-use and disposal issues following the spirit of good clinical practice (GCP).
- Many retrospective specimens are stored frozen or fixed and you need to know something about the stability of the candidate biomarkers in the storage conditions early on.
- In the case of pathological specimens the origin of the tissue needs to be taken into account. Control specimens have to show the same localization and the same characterization (e.g., age, ethnicity, environmental conditions),

and the form of preservation of the pathological and healthy specimens need have been performed with the same protocol. The same goes with specimens received from a biobank.

- The probability of making an erroneous conclusion decreases with the increased sample size and decreased extent of specimen picking. Although strictly selecting specimens with hindsight is necessary in the early phase of discovery, conclusions of the ability of a biomarker to discriminate between disease and non-disease should be made on specimens better representing the target population, i.e., individuals that have been or would be tested for the presence of disease. At this stage, many of the findings that first showed a good discrimination ability disappear, a natural phenomenon in the biomarker discovery pipeline.
- Blinding of specimens during the test process avoids bias especially in case of marginally positive subjects and is a required element in the later verification studies.

PITFALL:

Diagnostic sensitivity, diagnostic specificity, AUC (Area Under Curve in ROC, i.e. Receiver Operating Characteristic curve analysis), NPV (Negative Predictive Value) and PPV (Positive Predictive Value) calculations are not to be made on heavily selected specimens due to the strong bias.

TIPS ON CONDUCTING A COMPETITION ANALYSIS

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

To have commercial use, a novel IVD test needs to solve a true clinical problem and be backed-up by convincing evidence. But it also need somehow to be better compared to the competing approaches or add value to the existing testing sequence.

ALTERNATIVE BIOMARKERS AND ASSAY FORMATS

The competition analysis must span the entire spectrum of different approaches. Many diseases have multiple biomarkers due to the involvement of different biochemical pathways, and many biomarkers can be measured at different molecular expression levels.

BEST PRACTICES TO CONDUCT YOUR OWN COMPETITION ANALYSIS

- Describe the current practices (especially the golden standard) used as a routine in the clinic and their limitations.
- Conduct a literature search (both in scientific and patent databases) for alternative (competing) approaches to solve the above shortcomings. The search should include analysing all the alternative scientific and commercial applications for the same indication, irrespective of the biomarkers or technical platforms employed.
- It is important to recognize and describe the significant benefits of the new invention over the competing approaches. Acceptable advantages include, e.g.
  - → Increased diagnostic sensitivity and specificity,
  - → Earlier diagnoses (less advanced diseases with less complications),
  - → Earlier therapeutic actions (less costly treatment with better clinical outcomes),
  - → Improved convenience and patient compliance (e.g. less invasive sampling which is also likely to result in cost savings),
  - → Expected reduced number hospital admissions or length-of-stay,
  - → Cost savings in testing or other diagnostic procedures (by replacing or reducing more expensive testing and other procedures),
  - → Decreasing the number of invasive or harmful procedures,
  - → Encoding or hiding the exact solution allows communication on the non-confidential level (with care). An already filed patent application gives more freedom for the presentations but also postpones the feedback.
- If alternative applications do not exist, proceed with interviews of end users to ensure that the invention answers a topical and significant clinical question.
- Following the competition on regular (or even irregular) basis is important because new methods are constantly invented and singular surveys may give a false impression of non-existing competition. (Note that new patent applications become public only after 18-months.)
- Once a patent application is filed, the Office Actions (OAs) from patent authorities often contain valuable analysis of alternative solutions to the problem to be solved presented in the patent application. Re-visit the competition and FTO analyses to confirm that the advantages of the new method remain over the patent examiner's findings. (At least once a year).

BE AWARE THAT

- Competing applications are sometimes not recognized even though they were for the exact same indication and had the same performance and practicability characteristics. This is mainly because they are executed on a different technical approach or using biomarkers belonging to a different molecular class.
- Knowledge of competing methods emerges also during the patent prosecution process. Evaluation of competing methods should be made each time the patent authorities identify applications with same technical effect. Suggested time point for thorough evaluation is before entering the international Patent Cooperation Treaty (PCT) phase (evaluation then being based on the novelty and patentability report for the priority patent application) and national phase (evaluation then being based on the International Search Report (ISR) and Written Opinion (WOISA) or (at the latest) International Preliminary Report on Patentability (IPRP) of the PCT phase). The same decision making criteria is to be used than before submitting the application, i.e., a clear and relevant competitive advantage must remain.

AVOID SELF-COMPETITION

Sometimes the own improvements made after an own patent application compete with the markers and methods protected by the application. The new design is typically no longer patentable when the inventive subject matter has become public after 18 months.

In research projects spanning multiple years, postponing of patenting in the early years is recommendable if there is a high likelihood that the invention will be further developed or supplemented later (unless you already can predict the future developments, which is not often easy in case of new inventions). This allows ensuring that the most optimal embodiments are protected and offered for commercialization. However, postponing patenting also postpones publishing and one should have a strategy in place to optimize the schedule. Involve a patent attorney in planning the patenting strategy.

MAIN PREREQUISITES OF PATENTING

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

NOVELTY

Novelty means that an invention is different from earlier solutions disclosed in prior art. An invention cannot be patented if it has already been published by anyone, anywhere at the date of filing the patent application.

Publishing, and thereby forming an obstacle for novelty, refers to abstracts, posters, oral presentations (elsewhere than in internal closed meetings), articles, electronic and printed news, patent applications as well as brochures and marketing materials. It needs also be ensured that the data is not published accidentally (e.g., as presentation slides posted on a website after a closed meeting) or by an external party.

BEST PRACTICES:

- Performing a preliminary novelty search is important (also see chapters 5.1.1 and 5.2.2). A thorough novelty and patentability survey can be ordered from an external service provider once there is sufficient confidence based on an internal search.
- As the simplest first step, ask the researchers for their earlier publications (including abstracts, presentations etc.) as well as other closely related research by other groups. Search the researchers by name in the internet to find e.g. interviews or other public disclosures.

PITFALLS:

In academia, novelty is often destroyed by own publications that may come up only after a patent application is searched for novelty by the patent authorities. The publications (articles, abstracts, posters, public presentations) by the research team would need to be disclosed and reviewed more closely at the time of handling the invention disclosures.

INVENTIVENESS

Inventiveness means a non-obvious or even surprising (1 + 1 > 2) solution to a technical problem. An invention must not be evident for a person skilled in the art or be possible to achieve with basic optimization or routine trials.

PITFALLS:

Abstracts submitted to conferences are not considered very dangerous by the researchers if they have censored or coded the details. However, from the perspective of inventiveness, such a publication proves that a similar technical effect has been accomplished earlier. A patent application describing the invention in full may then be considered only to provide alternative markers for achieving the same technical effect than described earlier without details. This so-called non-enabling prior art is known for not destroying novelty but destroying inventiveness.

SCOPE OF PATENT PROTECTION

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

With the participation of Janni Wandahl Pedersen, European Patent Attorney, Partner Høiberg

- The most important characteristic of a patent is its scope of protection, which defines whether it can be easily circumvented or not – in other words, whether potential utilizers need a license for it or not.
- Broad patent claims are especially important in the case of university-based inventions for which the motivation for patenting lies in technology transfer, that is, selling or licensing the IPR for companies for a fee. This approach significantly differs from that of the industry, where the primary aim of patenting is typically not out-licensing but protecting the existing or upcoming products and/or increasing the value of the enterprise.
- From this perspective, some type of biomarker inventions are difficult to patent well.

BEST PRACTICES:

- To ensure that the university-owned IPR becomes interesting to companies, it is not enough to have an invention patented – it needs to be patented well and with broad enough patent claims so that the scope of protection is proper for the technology. Companies will only pay for rights they really need.
- If the intention is to form a start-up, the viewpoint of protecting the planned products can be emphasized somewhat more.
- Also make a plan for the relevant territorial coverage of the patent family.

THINGS THAT ARE DIFFICULT TO PATENT WELL:

- A weak patent is any patent that opens up the possibility for the potential utilizer to circumvent the patent claims by replacing the least meaningful limiting feature of the independent patent claim by another solution that works similarly well.
- Biomarker panels/patterns/signatures: The current evidence shows that many tests are likely to rely on multiple biomarkers in the future. It is, however, more complex to get regulatory approvals and solid patent protection for multiplex biomarker tests than the singular assays, as the more biomarkers that are required in the claim, the easier it will be for third parties to replace one or more of the biomarkers and thereby circumvent the patent
- Furthermore, the larger the number of markers in a combination, the easier it becomes to replace one marker with another (or several) outside the list. In the case only a pre-defined set of biomarkers ("signature") seems be patentable, preferably only the very top marker(s) absolutely needed for the method to work should be included in the independent patent claim(s). The remaining markers should be put in a priority order and listed in dependent claim(s). If the inventors only have an unprioritized list of candidate biomarkers that work in several different combinations, unity of invention will certainly be an issue and it will be difficult to obtain strong patent protection. This is also to avoid a "lack of unity" objection, which is easily received from the patent examiners when claiming an unprioritized list of biomarkers that work in several different combinations.
- Sequences: Nucleic acid and protein sequences typically have room for minor adjustments especially around the key binding units. It is difficult to protect complex nucleic acid or peptide sequences so that all solutions that work in an assay would be covered. In the case of new biomarker findings, it is important to try to search options for protecting the new assay by the target, without strictly defining the actual binders. The exact sequences should only act as examples and be described in the dependent claims. This also applies to new antibodies against existing biomarkers. The commercial value of antibodies easily replaceable by other antibodies (with slightly different sequences) is very low relative to patenting costs. Patenting of antibodies and nucleic acid assays is feasible only when the claims permit covering virtually any binders for the same.
- Methods for production of diagnostic assay: When use of a patented production method is not evident from the diagnostic assay itself or its public

documentation, infringements are difficult to monitor. The burden of proof is always at the IPR owner. The new method might result in significant savings in the manufacture of a specific product, but if the same could also be reached by other means, one could never be sure if the potential but reluctant client was already using the method or not.

- Patenting in the US: Due to a number of Court decisions over recent years, it is currently not possible to patent naturally occurring products in the US, such as naturally occurring nucleic acids, amino acid sequences and fragments thereof. It is defined by the patent authorities as "Law of Nature". It is however possible to patent variants of such naturally occurring products/sequences.
- In addition, it is also very difficult to patent diagnostic methods in the US unless the biomarker is measured by unconventional means and/or a post-solution activity is added to the claim, usually in the form of a treatment step with a specific drug (companion diagnostic claims).
- For all the above cases it needs to be noted that patent protection by research organizations is not pursued to ensure FTO of own products but the goal is in out-licensing. It is therefore very important that the patents cannot easily be circumvented because the customer is purchasing IPR, not the final product.

FREEDOM-TO-OPERATE (FTO) ANALYSIS

SOURCE: EXTRACT FROM BEST PRACTICES HANDBOOK, BIC PROJECT

With the participation of Janni Wandahl Pedersen, European Patent Attorney, Partner Høiberg

- Freedom-to-operate means not infringing the IPR rights (almost always patents) of others and not needing licenses – that may be costly or unavailable – for IP owned by third parties when commercializing the invention. For example, to use reagents (such as antibodies) in a commercial kit, one needs to agree with the provider that the use of the component in a commercial product is allowed. The cost may be different. Furthermore, one needs to make a survey that there are no existing method patents that would cover the use of the reagent in the same indication.

BEST PRACTICES:

- Compare the invention (as a whole) against existing patents and patent applications preferably already before generating own IPR. Pay special attention to key components that you cannot replace (such as rare antibodies).
- While FTO surveys can be purchased from several external actors, initial searches made by the inventors themselves increases their knowledge of the state-of-the-art and helps in not becoming dependent of IP owned by others in future projects. Purchased FTO surveys tend to be expensive (>10.000 €) and come therefore too late, i.e. when the product design is relatively fixed already.
- An initial FTO study should preferably be performed already after the early phase, before proceeding to assay development phase, so that obsolete or non-commercially-available (for further commercial use!) components or sequences are not used accidentally.
- Gaps in FTO detected any time before patenting may help in addressing the issue in the laboratory and in the patent application. In some cases alternative, free-to-use reagents and methods can be employed. If not, proceeding to pursue patent protection requires strong reasoning.
- Hindrances for FTO detected during patent prosecution must also be taken into account when making decisions on the continuance. Ask your patent attorneys to also report suspected FTO issues in their reports. Although not perceived as hindrances for patenting, they can be significant hindrances for commercialization.
- The need for third-party licenses should be allowed only rarely and only for elementary patents in which case a license is needed by all competitors, too.
- Take into account the expiry date and territorial coverage of the FTO-restricting patents.
- Note that some assays (such as nucleic acid assays) and chemistries (such as labelling reagents) can easily be executed with alternative technologies and chemistries although not familiar to the researchers. In such a case, the non-commercial proof-of-concept experiments may be based on a protected assay principle or chemistry. The commercialization partner can then execute the assay using the techniques and chemistries they prefer.

PITFALLS:

- An invention with restricted FTO means that the potential licensee also needs to negotiate and pay for other licenses before being able to commercialize the invention.

- For some fundamental technologies, commercial licenses may be readily available. The license fees for manufacturing and selling IVD assay kits are, however, significantly high compared to in-house or non-clinical assays such as animal or food safety testing.
- FTO may be compromised from the get-go if existing Background material is further developed in a publicly funded project where the project agreement (or MTA) limits the commercial use of so-forming Foreground materials/data. While an industry partner may suggest to retain all the rights to materials the company is supplying for the project, including the possible improvements made, the national laws typically prohibit subsiding private property with public funds. This means that the research organizations cannot (even by agreement) automatically transfer the industrial parties the right to commercially utilize the Foreground, but utilization can be separately negotiated at a market value price. However, the industrial partners may be offered the right of first refusal, i.e., priority of entering into an agreement (at market price) before external companies have been notified or approached. Similarly to above, the commercial utilization of other reagents, materials or software used in a research project may turn out to be prohibited. All restrictions and the potential to later violate third party rights need to be identified and tackled before the project starts.

HOIBERG – EUROPEAN PATENT ATTORNEYS (2020), PATENTING BIOMARKERS

Best route for BIOMARKER patenting

BIOMARKER:

- Measurable indicator of a physiological or pathological state
- Correlation between the read-out of the marker and the condition X

NEW CORRELATION

PATENT

- marker or parts thereof

...to assess condition X

KNOWN CORRELATION

PATENT

- Specific parts of the marker
- Specific detection means
- Specific marker levels
- Specific assay
- Specific analyte (tissue/body fluid...)
- Specific patient group
- Combination with other markers

...to assess condition X

SCIENTIFIC FINDING CONSIDER PATENTING

Identifying potential new inventions regarding BIOMARKERS

A **patient group** reacts differently	Problem with assay solved by adjusting **assay/ ingredients**	Statistics better when combined with **another marker**	**Sensitivity/ specificity** increases with antibody	A **new condition** is determinable with the assay	A **new sample type** is used
The specific level in this group	**The new assay**	**The combination of markers**	**The antibody or epitope for use in the assay**	**The new correlation**	**The diagnosis in this sample type**

CLINICAL PERFORMANCE CHARACTERISTICS

DEFINITIONS

DIAGNOSTIC SENSITIVITY AND SPECIFICITY

The **DIAGNOSTIC SENSITIVITY** (true positive rate) indicates the effectiveness of an IVD medical device in correctly identifying patients who have a particular disease or condition.

The **DIAGNOSTIC SPECIFICITY** (true negative rate) indicates the effectiveness of an IVD medical device in correctly classifying patients that do not have a particular disease or condition.

NOTE: The diagnostic sensitivity and diagnostic specificity depend on the choice of a cut-off value (e.g. to separate negative from positive values).

Prevalence of the disease targeted has a high impact on the accuracy of screening tests and diagnostic tests. A new biomarker test for a rare disease would have to be extremely accurate (specific) in order to not produce many false positive results amongst the high excess of not-affected people.

FOR EXAMPLE: The prevalence of a disease is about 20 cases/100 000 individuals, all of whom belong in the target population of the test. If you use an assay with 99 % diagnostic sensitivity and 99 % specificity, and test all the 100 000 individuals, you will probably catch all the 20 cases with the disease. However, if the diagnostic specificity of your assay is 99 %, you will get 1 % of false positive results, which is 1 000 cases. This means 50 false positives for each true positive case. If your diagnostic specificity is 95 %, you will get 5 % false positives, which is 5 000 cases, 250 for each true positive.

DIAGNOSTIC ACCURACY

The **ACCURACY** is the overall probability that a patient will be correctly classified.

PREDICTIVE VALUE

The **POSITIVE PREDICTIVE VALUE** indicates the effectiveness of an IVD medical device in separating true positive results from false positive results for a given attribute in a given population.

The **NEGATIVE PREDICTIVE VALUE** indicates the effectiveness of an IVD medical device in separating true negative results from false negative results for a given attribute in a given population.

NOTE: The expected predictive value depends on the prevalence of the disease or condition in the population of interest.

If the sample sizes in the positive (disease present) and the negative (disease absent) groups do not reflect the real prevalence of the disease, then the positive and negative predicted values, and accuracy, cannot be estimated and you should ignore those values.

Alternatively, when the disease prevalence is known then the expected positive and negative predictive values can be calculated.

CALCULATIONS

Disease / Test	Present (n)	Absent (n)	**Total**
Positive	True positive (a)	False positive (c)	**a+c**
Negative	False negative (b)	True negative (d)	**b+d**
total	**a+b**	**c+d**	**a+b+c+d**

Clinical performance characteristic	Formula
diagnostic sensitivity (true positive rate)	$\frac{a}{a+b}$
diagnostic specificity (true negative rate)	$\frac{d}{c+d}$
false positive rate	$\frac{c}{c+d} = 1 - \text{sensitivity}$
false negative rate	$\frac{b}{a+b} = 1 - \text{specificity}$
detected positive predictive value in the cohort[2]	$\frac{a}{a+c}$
detected negative predictive value in the cohort[2]	$\frac{d}{b+d}$
expected positive predictive value[2]	$\frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1\text{-specificity}) \times (1\text{-prevalence})}$
expected negative predictive value[2]	$\frac{\text{specificity} \times (1\text{-prevalence})}{\text{specificity} \times (1\text{-prevalence}) + (1\text{-sensitivity}) \times \text{prevalence}}$
diagnostic accuracy	$\frac{a+d}{a+b+c+d}$

2 – If the sample sizes in the positive (Disease present) and the negative (Disease absent) groups do not reflect the real prevalence of the disease, then the Positive and Negative predicted values, and Accucary, cannot be estimated and you should ignore those values.

Alternatively, when the disease prevalence is known then the expected positive and negative predictive values can be calculated.

MDCG 2019-7
Guidance on Article 15 of the Medical Device Regulation (MDR) and *in vitro* Diagnostic Device Regulation (IVDR) regarding a 'person responsible for regulatory compliance' (PRRC)

MANUFACTURERS1 (PARAGRAPH 1)

Manufacturers shall have available within their organisation at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of medical devices. The requisite expertise shall be demonstrated by either of the following qualifications:

- **a.** *a diploma. certificate or other evidence of formal qualification. awarded on completion of a university degree or of a course of study recognised as equivalent by the Member State concerned. in law. medicine. pharmacy. engineering or another relevant scientific discipline, and at least one year of professional experience in regulatory affairs or in quality management systems relating to medical devices;*
- **b.** *four years of professional experience in regulatory affairs or in quality management systems relating to medical devices.*

Without prejudice to national provisions regarding professional qualifications. manufacturers of custom-made devices may demonstrate the requisite expertise referred to in the first subparagraph by having at least two years of professional experience within a relevant field of manufacturing:

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1 Enterprises which employ at least 50 persons and whose annual turnover and/or annual balance sheet total exceeds EUR 10 million (Commission Recommendation 2003/361/EC of 6 May 2003)

Clarification on qualifications

It shall be noted that:

- For the purpose of fulfilling the requirement laid down in point 'a' of Article 15 (1), any qualification acquired outside the EU, including any university diplomas or certificates, should have been recognised by an EU Member State as equivalent to the EU corresponding qualification.
- *Professional experience in regulatory affairs or in quality management systems relating to medical devices* should be related to the EU requirements in the field.

Meaning of "Within their organisation"

The person responsible for regulatory compliance (PRRC) appointed would need to be an employee of the organisation.

Organisations with more than one legal manufacturer

Organisations with more than one legal manufacturer under the parent company would need to ensure that each legal manufacturer has its own PRRC.[2]

Can the PRRC be located outside the EU?

As to the location of the PRRC, it is important that a close linkage, of a permanent and continuous nature, is established between the PRRC and the manufacturing activities. For this reason, for manufacturers located outside the EU, it must be assumed that the PRRC should also be located outside the EU. On the other hand, for manufacturers located in the EU, it must be assumed that the PRRC should also be located in the EU.

MICRO AND SMALL MANUFACTURERS[3] (PARAGRAPH 2)

Micro and small enterprises within the meaning of Commission Recommendation 2003/361/EC shall not be required to have the person responsible for regulatory compliance within their organisation but shall have such person permanently and continuously at their disposal".

Meaning of "permanently and continuously at their disposal"

The micro or small enterprise may subcontract the responsibilities of a person responsible

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2 In the context of Article 15, the obligation for having available within the organisation at least one PRRC refers to the individual legal manufacture.

3 Enterprises which employ fewer then 50 parsons and whose annual turnover and/or annual balance sheet total does not exceed EUR 10 million (Commission Recommendation 2003/361/EC of 6 May 2003)

for regulatory compliance to a third party, so long as the qualification criteria is met and the manufacturer can demonstrate and document how they can meet their legal obligations. For example, the PRRC may be part of an external organisation, with which the manufacturer has established a contract laying down provisions so as to ensure the permanent and continuous availability of that party. The contract should mention the relevant person's qualifications allowing compliance with points a and b of Article 15 (1).

Can the PRRC be located outside the EU?

For micro or small enterprises located in the EU, it must be assumed that any person to be permanently and continuously at their disposal should be also located in the EU.

AUTHORISED REPRESENTATIVES (PARAGRAPH 6)

Authorised representatives shall have permanently and continuously at their disposal at least one person responsible for regulatory compliance who possesses the requisite expertise regarding the regulatory requirements for medical devices in the Union. The requisite expertise shall be demonstrated by either of the following qualifications:

- **a.** *a diploma, certificate or other evidence of formal qualification, awarded on completion of a university degree or of a course of study recognised as equivalent by the Member State concerned, in law, medicine, pharmacy, engineering or another relevant scientific discipline, and at least one year of professional experience in regulatory affairs or in quality management systems relating to medical devices;*
- **b.** *four years of professional experience in regulatory affairs or in qualify management systems relating to medical devices.*

Meaning of "permanently and continuously at their disposal"

The authorised representative may subcontract the responsibilities of a person responsible for regulatory compliance to a third party, so long as the qualification criteria is met and the authorised representative can demonstrate and document how they can meet their legal obligations. For example, the PRRC may be part of an external organisation with which the authorised representative has established e a contract laying down provisions so as to ensure the permanent and continuous availability of that party. The contract should mention the relevant person's qualifications allowing compliance with points a and b of Article 15 (1).

Can the PRRC be located outside the RP

Taking into account that the Authorised Representative is located in the EU, it must be assumed that any person to be permanently and continuously at its disposal should be also located in the EU.

ROLES AND RESPONSIBILITIES OF THE PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE WITHIN A MANUFACTURER (PARAGRAPH 3)

For the purpose of this position paper, the roles and responsibilities of a PRRC have been cross-referred to the roles and responsibilities of a manufacturer, as stated in Article 10 of the MDR and IVDR. This paper does not interpret the roles and responsibilities of a PRRC. We recommend that any guidance on post-market surveillance, vigilance, clinical investigations and performance studies, created at a European level, should cross-refer to Article 15, paragraph 3 to provide guidance on what a PRRC of a manufacturer would be expected to do in these areas.

The person responsible for regulatory compliance shall at least be responsible for ensuring that:

a. *the confomity of the devices is appropriately checked, in accordance with the quality management system under which the devices are manufactured, before a device is released:*

Manufacturers "of devices other than investigational (performance study) devices, shall establish, document, implement, maintain, keep up to date and continually improve a quality management system that shall ensure compliance with this Regulation in the most effective manner and in a manner that is proportionate to the risk class and the type of device" (Article 10(9) of the MDR and Article 10(8) of the IVDR).

b. *the technical documentation and the EU declaration of conformity are drawn up and kept up-to-date*

Manufacturers "(of devices other than custom-made devices) shall draw up and keep up to date technical documentation for those devices" (Article 10(4) of the MDR and IVDR) and "shall draw up an EU declaration of conformity" (Article 10(6) of the MDR and Article 10(5) of the IVDR).

c. *the post-market surveillance obligations are complied with in accordance with Article 10(10) (Article 10(9) of the IVOR);*

Manufacturers "of devices shalt implement and keep up to date the post-market surveillance system" (Article 10(10) of the MDR and Article 10(9) of the IVDR).

d. *the repotting obligations referred to in Articles 87 to 91 (Article 82 and 86 of the IVOR) are fulfilled*

Manufacturers "shall have a system for recording and reporting of incidents and field safety corrective actions as described in Articles 87 and 88" (Article 10(13) of the MDR and Article 10(12) of the IVDR).

e. *in the case of investigational devices, the statement referred to in Section 4.1 of Chapter 11 of Annex XV (Section 4.1 of Annex XIV of the IVOR) is issued.*

Manufacturers shall ensure that "a signed statement by the natural or legal person responsible for the manufacture of the investigational device [for performance study] that the device in question conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation [performance study] and that, with regard to those aspects. every precaution has been taken to protect the health and safety of the subject."

ROLES AND RESPONSIBILITIES OF THE PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE WITHIN AN AUTHORISED REPRESENTATIVE (PARAGRAPH 3)

The PRRC of an AR should be responsible for ensuring that the tasks of an AR as specified in the given mandate, in accordance with Article 11(3), are fulfilled.

Can one individual be the PRRC for a manufacturer and its authorised representative?

The person responsible for regulatory compliance for an authorised representative and for an 'outside EU' manufacturer cannot be the same person. There is a clear desire within the Regulations for the authorised representative to be adding an additional level of scrutiny and ensure that the supervision and control of the manufacture of devices, and the relevant post-market surveillance and vigilance activities are adequately effected. If the two roles were conducted by the same person, the additional level of scrutiny would be undermined.

For the same reason, the PRRC of a micro or small enterprise and the PRRC of the authorised representative of that same enterprise shall not belong to the same external organisation.

FACTSHEET FOR AUTHORISED REPRESENTATIVES, IMPORTERS AND DISTRIBUTORS OF IVD MEDICAL DEVICES

https://ec.europa.eu/health/md_newregulations/overview_en

UDI SYSTEM UNDER THE EU REGULATIONS 2017/745 AND 2017/746 https://ec.europa.eu/health/

Basic UDI-DI & UDI-DI attributes

BASIC UDI-DI SET OF DATA IN UDI DATABASE

Principle: Each UDI-DI inherits the attributes of its linked Basic UDI-DI and devices DI

BASIC UDI-DI

Mandatory

- Applicable legislation (IVDR) (*)
- 2. Basic UDI-DI value (*)
- 2b Basic UDI-DI Issuing entity (*)
- 6. Manufacturer SRN (*)
- 5. Name and address of manufacturer
- 9. Risk class (*)
- A.2.14 Intended for self-testing (Y/N) (*)
- A.2.14 Intended for near-patienttesting (Y/N) (*)
- Companion diagnostics (Y/N) (*)
- Instrument(Y/N) (*)
- Reagent(Y/N) (*)
- Professional testing (Y/N) (*)
- 11. A. Name and/or, if applicable, device model that identifies the device(s) with this BASIC UDI-DI in the technical documentation and/or certificate or declaration of conformity

Mandatory if applicable

- 7. Name and address and SRN of AR

(Name and/or model shall be provided)

UDI-DIS

Mandatory

- 0. UDI-DI value (*)
- 0b. UDI-DI Issuing entity (*)
- 11.B. Reference, Article or Catalogue number (*)
- Device with Direct marking (Y/N) (*)

- 1. Quantity of device(s) (*)
- 3. Type of UDI-PI (*)
- 15. Labelled as single use (YN) (*)
- 17. Device labelled sterile (Y/N) (*)
- 18. Need for sterilisation (Y/N) (*)
- 8. Medical device nomenclature (CND) code (1)
- 21. Status

Mandatory if applicable

- Direct marking UDI-DI value (*)
- Direct marking UDI-DI issuing entity (*)
- 4. Unit of use UDI-DI (*)
- 13. Storage/handling conditions
- 10-14. Name(s)/Trade name(s) (including languages)
- 16. Maximum number of reuse (*)
- 20. Critical warnings or contra-indications
- 27 (A.2.10). In the case of devices designed and manufactured by another legal or natural person as referred in Article 10(14), the name, address and contact details of that natural/legal person

Optional

- Secondary DI (value and issuing entity)
- 12. Additional product description
- 19. URL for additional information

UDI-DIS (CONTAINER PACKAGE DI)

Mandatory

- 0. UDI-DI value (*)
- 0b. Issuing entity (*)
- 1. Quantity per package (*)
- 21. Status

(1) Nomenclature decision: https://ec.europa.eu/doc sroom/documents/34264

Other Device Data attributes

BASIC UDI-DI

Mandatory

- A.2.5 Presence of Human tissues/Cells (Y/N) (*)
- A.2.6 Presence of Animal tissues/Cells (Y/N) (*)
- A.2.7 Presence of Substances/cells of microbial origin (Y/N) (*)
- Kit (Y/N) (*)

Mandatory if applicable

- A.2.9 Performance study IDs (..link)

Provided by NB or for certificate ID under Art 26(2) provided by manufacturer and confirmed by NB

- A.2.2 Certificate IDs (with NB, type .. Link)
- A.2.11 SSP;

UDI-DIS

Mandatory

- A.2.13 New Device (Y/N) (*)
- A.2.3 Member State of the Placing on the EU Market of the Device (*)

Mandatory if applicable

- A.2.4 Member State(s) where the Device is made available in the Country

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Version April 2019 (*) may not be changed

FACTSHEET FOR AUTHORISED REPRESENTATIVES, IMPORTERS AND DISTRIBUTORS OF IVD MEDICAL DEVICES

https://ec.europa.eu/health/md_newregulations/overview_en

Definitions

AUC (AREA UNDER THE CURVE): It is the mathematical calculation of the definite integral between two points on a graph and represents the overall ability of the test to discriminate between those individuals with the disease and those without the disease. A truly useless test (one no better at identifying true positive than flipping a coin) has an area of 0.5. A perfect test (one that has zero false positives and zero false negatives) has an area of 1.0.

BIOMARKERS: a molecular 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, the presence, absence or concentration of which is measured in a analytical procedure such as by a laboratory test to obtain information on an individual's health status. The biomarker (or analyte) can e.g. be a nucleic acid, protein, polysaccharide or metabolite.

CLINICAL SIGNIFICANCE: the practical importance of a scientific observation. It is used as a tool to quantitatively assess whether the magnitude of an observed difference is such that it is relevant to patients. Measures include e.g. effect size and risk ratios. In comparison, statistical significance refers to the likelihood of a difference being observed due to chance.

FTO (FREEDOM- TO-OPERATE): analysis whether it is commercially "safe" to make or sell a product in the country, without infringing existing third-party rights.

LINEAR MEASURING RANGE: the range spanning from the analytical detection limit to the highest concentration falling in the linear part of the calibration curve.

NDA (NON -DISCLOSURE AGREEMENT): it is a signed agreement between two parts to protect the confidentiality of any trade secrets or similar information revealed during their dialog.

PRODUCT: generally "something that is made to be sold, usually something that is produced by an industrial process or something that is cultivated". In the BIC project the term refers to a physical IVD test (i.e. assay) kit for measuring biomarker(s) or analyte(s) in selected clinical settings (including home and near patient testing).

PPV (POSITIVE PREDICTIVE VALUE): the probability that all the positive test results are truly positive.

ROC (RECEIVER OPERATING CHARACTERISTICS): It is a graphical representation curves, often used to illustrate the connection/trade-off between clinical sensitivity and specificity for every possible cut-off for a test or a combination of test. In addition, the area under the ROC curve gives an idea about the benefit of using the respective test(s).

STAKEHOLDERS: in biomarker commercialisation include e.g. research organizations, health care providers (e.g. hospital and clinical laboratories), clinicians, patients, IVD industry, investors and health insurance companies.

NOTES

NOTES

Translating biomarker inventions into an in vitro diagnostic (IVD) ready for the market is a complex endeavor, that requires time and resources as well as a structured process to obtain a product with the required regulatory approvals. The Biomarker Commercialization (BIC) Guide provides guidance to academic and/or clinical researchers, technology transfer officers (TTOs) and small and medium enterprises (SMEs) throughout the biomarker development process from the discovery to the launch of the product on the market.

This book covers the clinical, regulatory, and business aspect of the commercialization process standing on the different technology readiness levels (TRL) of your biomarker discovery. The process is presented as a list of tasks, comprehensively described and partially supported by useful, downloadable documents and links. This published version follows a linear and simplified presentation of a cyclical and iterative process. As such, implementation of this guidance should be adapted to the user's reality and should not prevent them to re-assess the progress or level accordingly to their specific project.

Use the BIC Guide also to prepare questions for an informed discussion with your partners and collaborators.

We recommend that until there is no strategy for securing your Intellectual Property, do not publish, share, present or disclose your discovery. Doing so could severely restrict the scope of and the ability to patent.

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LABMASTER medical devices

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