Tools for Biomarker Commercialization

The BiC Project

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BIC Project partners and Funding

- A transnational cooperation of 3 research and 5 cluster organizations in the Baltic Sea Region:

  Denmark (Coordination: Aalborg University Hospital)
  Germany
  Poland
  Finland
  Estonia
  Lithuania

- Project budget is EUR 2,55 million and it is co-financed by the European Regional Development Fund through the Interreg Baltic Sea Region Programme with EUR 1,96 million.

BIC – the goal of the project

Challenges identified

- How do you translate a biomarker discovery from lab to clinical setting?
- How to ensure efficient validation phase and generation of valid data?
- How to ensure that the researchers have adequate knowledge about the commercialization of biomarkers?
- How does a TTO select the best biomarkers projects for commecialization?
- How to provide industry or investors relevant documentation

Interview conclusions, Researchers

- Researchers generally had **limited experience** with **commercialization**
- Researchers are well aware of the technical requirements for a biomarker
- Regulatory aspects are not generally occupying the researchers
- **Researchers would benefit of guidance and training in e.g. IPR and regulatory issues,** systematic product development and making market and competition analyses

- Suggestions for TTOs from researchers:
  - Organizing mentoring, training, expert services (validation process, regulatory aspects)
  - Organizing networking with companies and end-users
  - A clear roadmap on biomarker development with relevant guidelines

Interview Conclusions – Large Companies

- Development of biomarkers is exclusively based on **market and clinical needs and cost benefit analyses**
- Only biomarkers that are patented with a demonstrated proof of concept fulfill the criteria for entering into a collaboration
- The large drug development companies are continuously scouting to find interesting biomarker projects
- The **drug development companies are willing to collaborate, at least after a patent has been granted, as well as validation and proof of concept**.
- Today there seem to be a development gap between the identification of a biomarker and the clinical validation.

Interview Conclusions - SMEs

- The main steps for biomarker development should be – to pick the right methodology, find freedom-to-operate or protect the IP, develop the assay, then validate it and develop a sustainable business model.
- **Keep reimbursement in mind,** to get back the money invested
- **Difficult to get into clinics** since doctors are busy and no clear path exists
- Difficult to access clinical samples
- A **marker should fit to already existing workflows** on the technological and clinical level.
- IP is important, either one's own or via access through licensing.
- A matchmaking tool would be good

Interview Conclusions – End Users

- **Challenges** in taking a new biomarker into use in clinical practice include: Price, Availibility, Lack of competencies + **time to convince clinicians** and other key stakeholders of the biomarker´s usefulness
- Biomarker **assays must include** a clear medical need and demonstrated usefulness (**health benefits, proven added value**) – as well as good and sufficient clinical validation
- Common economic aspects include: high unmet medical need, benefit of new biomarker test, average price of the most common tests is under ten euros, Health Insurance Companies often pay for diagnostics – reimbursement is crucial
- To get the CE mark takes much time (years); **in-house test´s validation takes less time (months)**

Interview Conclusions – TTO's

- The TTOs have different experience in commercializing biomarkers and all agree that currently there is no proven successful pathway for this.
- Guidelines ensuring that researchers become aware of the basic demands for commercialization in the early phases of their research are needed
- **The key issue include the timing related to patent application (national phases) and validation requirements**. But to commercialize a biomarker, you need to have a patent
- Often it would be better to **wait with the patent application to** get sufficient **validation**, but this often conflicts with the **researchers' wishes to publish**

Interview Conclusions - Investors

- **Biomarker area** is developing fast, but it **is difficult because of lacking information** and thus it being **hard to convince the industry**
- ROI is very important to address – the patenting process is very costly
- Main patent areas: UK, Germany, France, Japan, USA. Investors nowadays consider also China and India
- Big companies are not interested in the early stage of development, so potential investor should be prepared to address the regulatory challenges

Interview Conclusions – Cluster Organisations

- Biomarkers rarely a specific focus area. Clusters may play a role in national/regional agenda setting promoting biomarkers potential
- **Reimbursement - Despite CE regulation**, **each country has own additional rules**
- High cost of biomarkers not a hinder if benefits are even larger
- **Marketing and QA underestimated**. Cultural barriers between research and industry and between research and hospitals significant. Only very few good cases on biomarker development reaching the market.

BiC - Achievements

- **BIC Guide Tool incl. Self evaluation tool**
- **A Best Practice Handbook**
- **Screening and Selection guide for TTO's**
- Guidelines for Regulatory Requirements

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BIC BIOMARKER COMMERCIALIZATION

The BIC Guide

BIC Guide: main features

- Creates overview of the process
- 7 phases (TRL based) 3 tracks. A list of tasks
- Support documents for specific tasks
- Check list and self evaluation tool at the end of each phase
- Link to useful material

However: Only the 5 first phases covered at this stage (research phases)

The BIC Guide (BIC Master Tool) Test version

https://bicmastertool.nu/flow/bic-master-tool/

The BIC Guide (MasterTool) - Overview

Research phase

1. Biomarker discovery
TRL-1 Basic principles observed

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

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

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

Technology transfer

5. Pre-industrial maturation phase
TRL-5 Configuration to industrial application (beta prototype)

TRL-6 Technology demonstraded in relevant environment

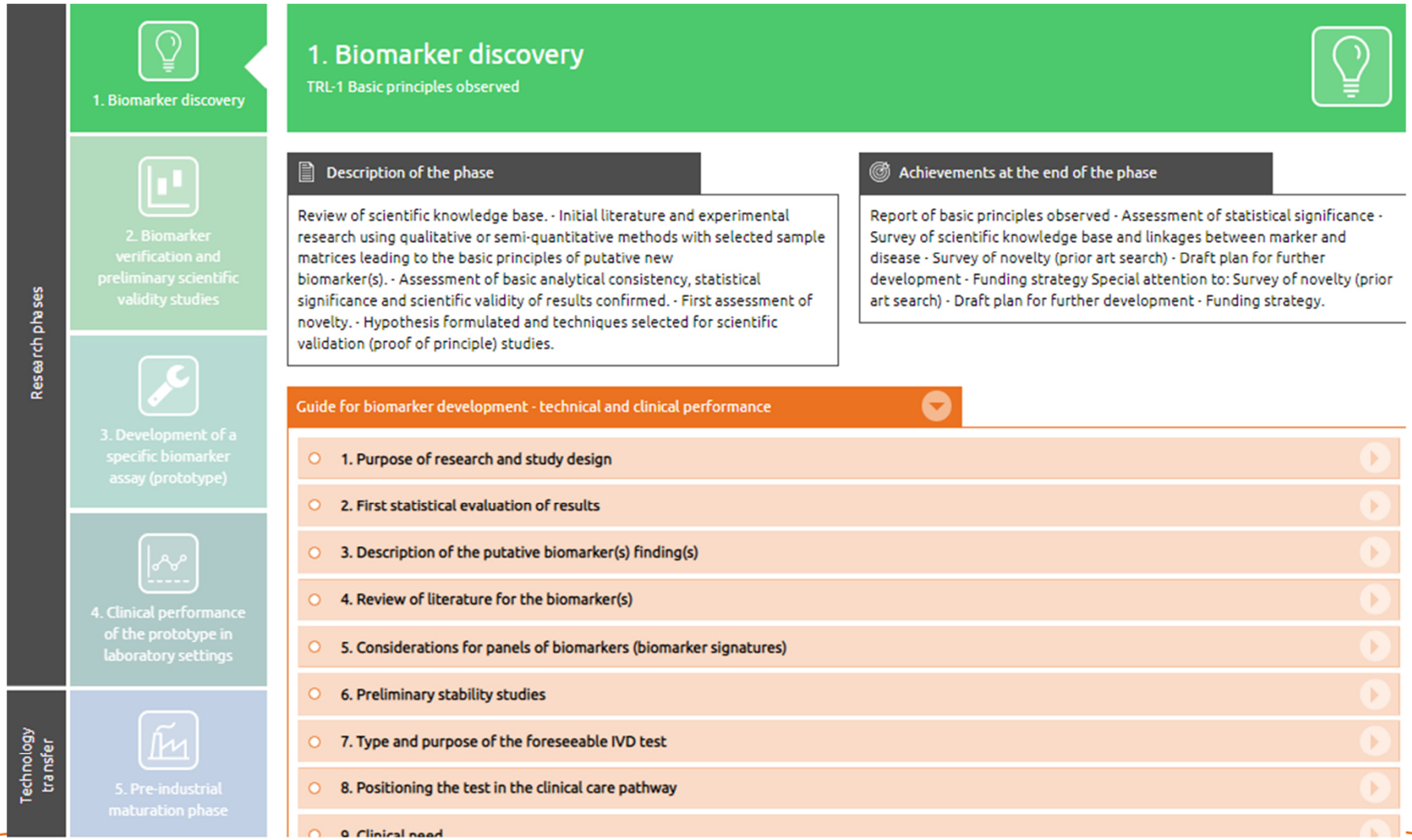
Industrial and market phase

6. Industrial assay development
TRL-7 Clinical validation of IVD assay

7. Commercial launch and clinical implementation
TRL-8 Commercial launch of IVD assay

TRL-9 Post launch monitoring of IVD assay

The BIC Guide (MasterTool) - Overview



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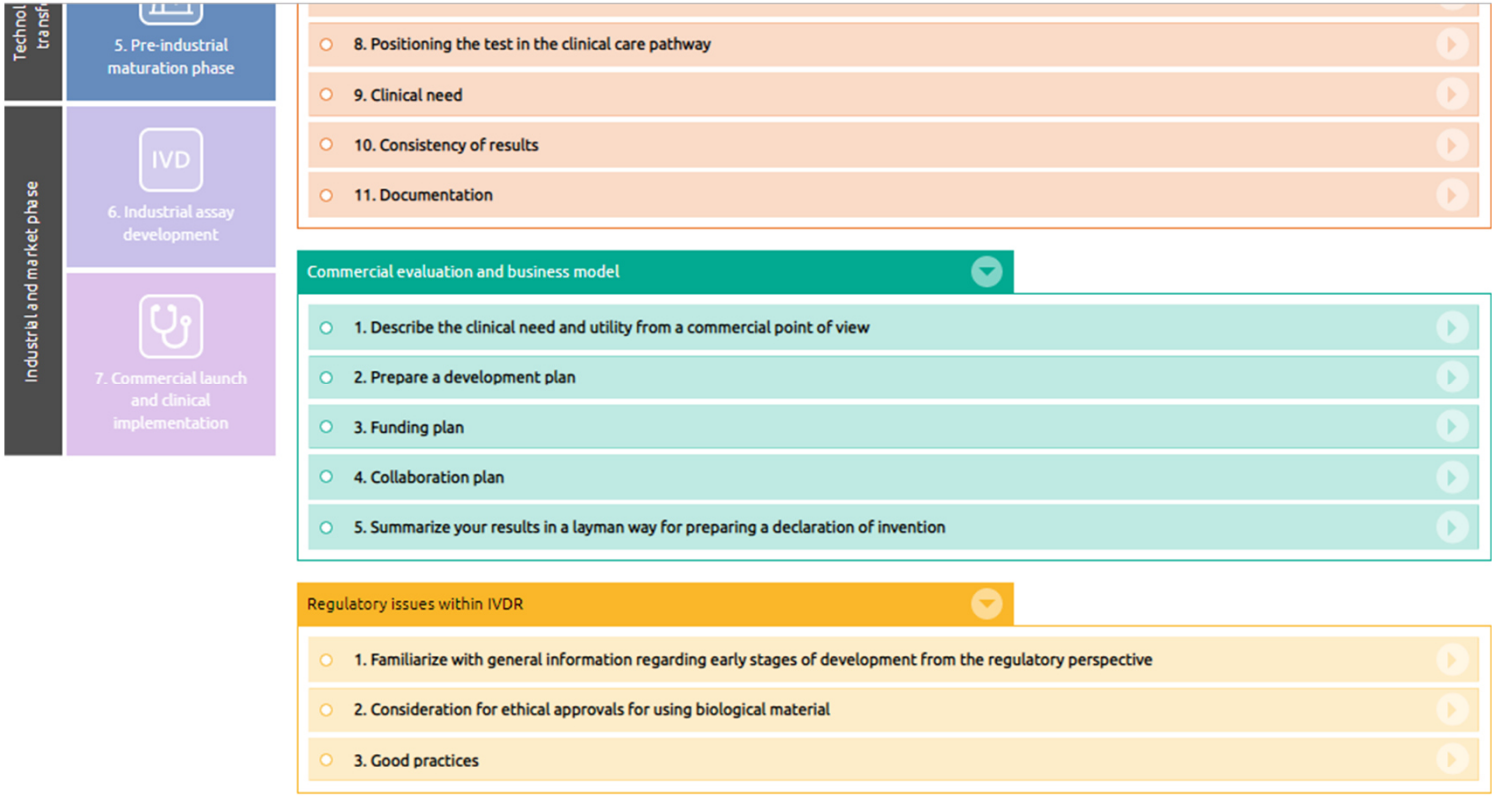
The BIC Guide (MasterTool) - Extractions



The BIC Guide (MasterTool) - Extractions

Indu

7. Commercial launch and clinical implementation

- 2. Prepare a development plan
- 3. Funding plan
- 4. Collaboration plan
- 5. Summarize your results in a layman way for preparing a declaration of invention

Regulatory issues within IVDR

- 1. Familiarize with general information regarding early stages of development from the regulatory perspective

Explanation of the task and expected outcome

Stages of IVD assay commercialization process that do not involve participation of a company (early stages of development) do not contain mandatory regulatory tasks regarding placing product on the market (required by IVDR). A researcher has to take into account the regulatory pathway that biomarker products have to go through, but he/she is not legally responsible for it. Therefore, tasks concerning regulatory aspects at early stages were developed at the basis of good practices. Application of those would potentially improve pace of industry assay development (fulfil legal enterprise obligations), and in result place product on the market.

Task related material (links and downloads, task related good practices)

Link to IVDR:

eur-lex.europa.eu/legal-content/EN/TXT/

- 2. Consideration for ethical approvals for using biological material
- 3. Good practices

The BIC Guide testing phase

- In the periode from 1 October 2019 to the end of march 2020, a selected group of **researchers, SMEs and TTOs** in the Baltic Sea Region (BSR) have tested the *BIC Guide* developed by the BIC Consortium. This tool provides guidance through technical, clinical, commercial and regulatory aspects of biomarker commercialization process.

- Based on the results collected from the test phase, the *BIC Guide* is currently revised and a final version will be **available to the public free of charge in summer 2020.**

- By enabling better and more efficient commercialization of biomarkers, the overall output of the BIC project will contribute in improving realization and competitiveness of biomarkers discoveries primarily within BSR.

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BIC Guide: main feedback

- to be integrated in the final version

- „ The items are great! They serve as good reminders for any scientists in the field.“ (Finnish researcher)
- „Very, very useful for any scientist. There are lots of things we are going to include in our future processes and projects.“ (Finnish researcher)
- „The online tool is very intuitive and easy to use. The content is very fine, meaningful and helpful.” (Danish researcher)
- „The regulatory track is not very close to scientists.” (Finnish researcher)
- „However the commercialization and regulatory tracks may overload the researchers. We probably would not look at those very much.“ (Finnish researcher)
- “We are not familiar with regulatory tasks, and there is very little interest to getting closer to them, as long as the necessity to apply them belongs to another group.” (Danish researcher)
- “There has to be a perfect conformity between regulations and regulatory descriptions in MT in order to really make the tool usable.”

The BIC Guide (MasterTool) – Expectation and first impressions

- Main Expectations / expected benefit
  - Structured overview of the BIC process
  - A good list of activities which needs to be done in the commercialization of new biomarkers.
  - Comprehensive informational material regarding the BIC process
  - Time savings for searching for information on different aspects of biomarker development
- First impressions on the BIC MasterTool
  - First tool to support the commercialization pathway in such comprehensive way
  - Well structured, designed and self-explanatory

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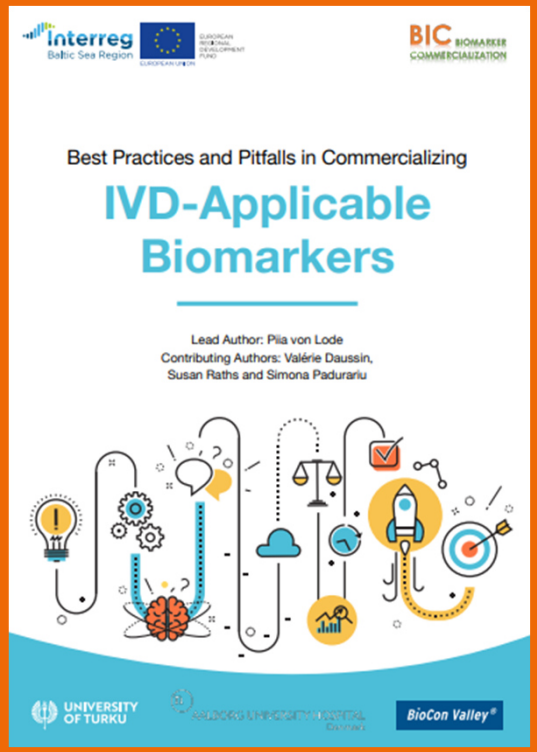
BIC Best Practices Handbook



BIC Best Practices Handbook: main chapters

CLINICAL IMPACTS OF IVD-APPLICABLE BIOMARKERS

THE IVD-APPLICABLE BIOMARKER PIPELINE

COMMERCIALIZATION ASPECTS

INTELLECTUAL PROPERTY RIGHTS (IPR)

BUSINESS MODELS, AGREEMENTS AND OTHER LEGAL VIEWPOINTS

BIC Best Practices Handbook: extractions

SCOPE OF PATENT PROTECTION

The most important characteristic of a patent is its scope of protection, which defines whether potential utilizers need a license for it or not.

Broad patent claims are especially important in the case of selling or licensing the IPR for companies for a fee. In the industry 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.

Best practices:

- To ensure that the university-owned IPR becomes interesting to companies: it needs to be patented well and with broad enough patent claims
- 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 territorial coverage of the patent family.

Things that are difficult to patent well: etc…

BIC Best Practices Handbook: extractions

FREEDOM TO OPERATE (FTO)

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.
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: ……

BIC Best Practices Handbook: extractions

TIPS ON CONDUCTING A COMPETITION ANALYSIS

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

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.
- 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)
    - Improved convenience and patient compliance
    - Expected reduced number hospital admissions or length-of-stay

BIC Best Practices Handbook: extractions

INTELLECTUAL PROPERTY RIGHTS (IPR) in early stage projects

Most commercial partners will not consider licensing without respective intellectual property (IP) protection due to the competitive edge it provides. The existence of IP rights (IPR) is paramount also in the eyes of investors.

Furthermore, concrete IPR allows ensuring a share of profits to both the inventors and the research organization after the launch of the product.

Using patents as a source of information

Approximately 70-85 % of information found in patent databases cannot be found elsewhere. Researchers that follow the patenting field will have a significant advantage compared to those who are not up-to-date on the newest directions of commercial development.

Patenting versus publishing: alternative protection strategies for early phase inventions

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Screening and Selection Guide for TTO's

BIC Screening and Selection Guide for TTO's

Characteristics of the biomarker(s)

- Name(s), synonym(s), acronyms and all different codes of the biomarker(s):

  _____

- Disease/condition under investigation:

  _____

- Applicable molecular forms:
  - ✓ DNA
  - ✓ mRNA
  - ✓ other, e.g. modification of polynucleotide: _____
  - ✓ protein
  - ✓ modification of a protein (e.g. glycovariant): _____
  - ✓ metabolite
  - ✓ other, which:_____
- Sample matrixes accepted:

  _____

- Stability of the biomarker in above matrixes (RT, -20 °C, freeze-thaw cycles, recovery-% etc.):

BIC Screening and Selection Guide for TTO's

Description of the IVD test planned

- Test type
  - ✓ Diagnostic
  - ✓ Prognostic
  - ✓ Predictive, for which therapy:
  - ✓ Screening
  - ✓ Risk/susceptibility
  - ✓ Companion diagnostics, for which drug:
  - ✓ Non-IVD applicable marker, specify type of use:
  - ✓ Other:_____
- Intended purpose of the test:

  _____
- Is the test able to detect the disease at an early stage?
  - ✓ Yes, before clinical symptoms
  - ✓ Yes, directly after onset of the acute disease
  - ✓ No
    - If no, can the disease yet be successfully treated at the time of positive test result?

BIC Screening and Selection Guide for TTO's

Target population

- Prevalence of the disease/condition in (different) population(s):
  _____
- Who would be tested:
  - ✓ Entire population
  - ✓ Specific subgroup of the population, which:_____
  - ✓ Entire population of the sick (with already established diagnosis)
  - ✓ Specific population of the sick, which:_____
    - Share amongst all sick: _____ %
  - ✓ Newborn
  - ✓ Adults with age range of: _____
  - ✓ Elderly
  - ✓ Female
  - ✓ Male
  - ✓ Specific ethnicities:_____
  - ✓ Specific timing or other trigger of testing, when:_____
- Contraindications for testing, which/when:

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Guidelines for regulatory process

BIC Guidelines for regulatory process

BIC Guidelines for regulatory process

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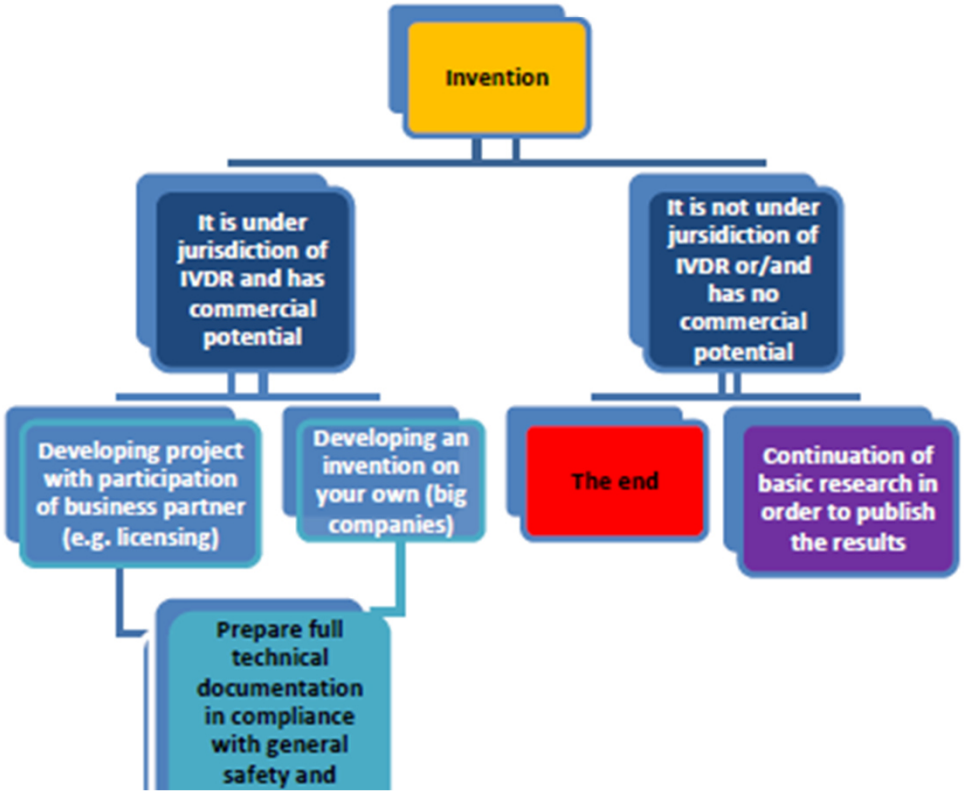
BIC Guidelines for regulatory process

3.5 Biomarker commercialization process – general regulatory process

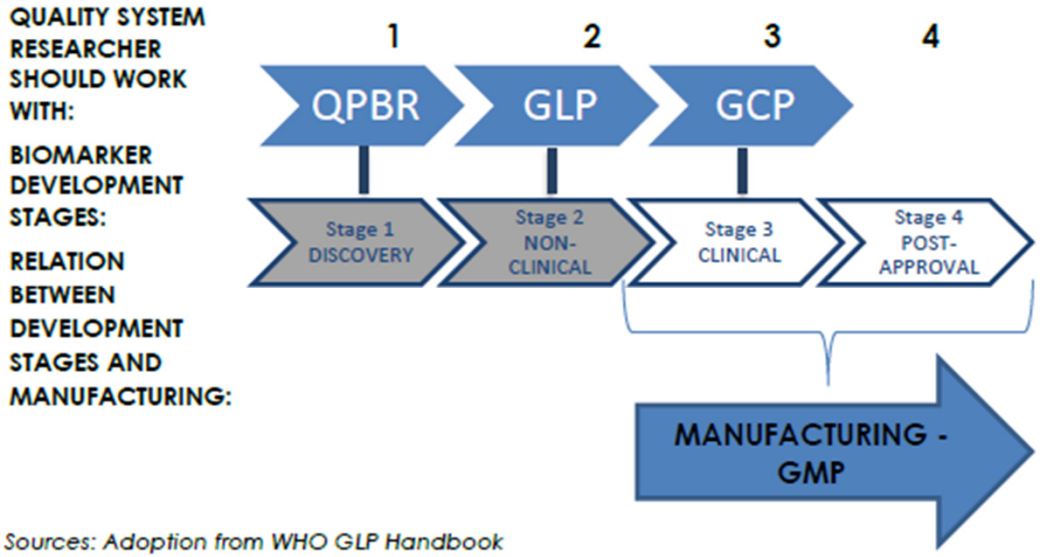
Figure 4: Biomarker assay commercialization process from regulatory point of view (on the basis of IVDR) – from invention to the market implementation - general scheme



BIC Guidelines for regulatory process

quality system recommended to researchers. Detailed GLP information can be found in Annex IV of Regulatory Guide and in GLP handbook released by WHO: https://www.who.int/tdr/publications/documents/glp-handbook.pdf .

Figure 8: Relation between non-clinical studies stages and quality systems recommended to work with by researchers/manufacturers



Sources: Adoption from WHO GLP Handbook

Key:

Stages in biomarker development concerning **Researcher** (biomarker commercialization value chain member context).

Thank you for your attention !

More information: biomarker.nu

https://www.linkedin.com/company/bic-biomarker-commercialization

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