Considerations from Developer's Perspective on the Opportunities for Alignment of Development between Drugs and Diagnostics

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Precision Medicine

As our understanding of the molecular mechanisms of disease and corresponding treatment modalities are increasing, targeted therapy approaches are gaining increasing relevance.

As a result, biomarker tests are becoming an integral part of drug development.

Overview of the Activities of the EBE EFPIA PMWG

- **Evidence based analysis of the benefit of personalised medicines**
- **Regulatory requirements for investigational use of biomarker tests**
- **Implementation of the IVD Regulation**
- **Novel technologies: Next Generation Sequencing**

The Benefit of Personalised Medicines

Evidence Based Analysis of the Benefit of Personalised Medicines

- Targeted and personalised interventions have led to better patient outcomes and optimized regimens
- Better patient management is associated with savings to healthcare systems and society and for resources to be used more efficiently
- PM directly impacts clinical trial design and patient recruitment
- Currently different adoption models with varying degree of access to PM in EU

Recommendations to Improve Equitable Access to PM

- **National policy to ensure prioritisation of PM should work hand in hand with existing health strategic plans** (e.g. National Cancer Plans).
  - The level of resources and funding needs to be aligned to aspirations and the strategy should articulate the genomic profiling strategy.

- **Continued emphasis is needed on better management of care, consolidating expertise and resources to ensure the adequate 'personalisation of care'.**
  - This can be achieved through a centralised approach (i.e. developing 'centres of excellence') or via cross-functional collaboration through healthcare networks.

- **National governments should continue investing and cooperating in next-generation testing infrastructure (such as molecular genetics labs) as well as developing dedicated funding pathways to ensure access to diagnostics.**

- **Collecting data to track access to diagnostics (and making this public) as well as putting a greater emphasis on External Quality Assessments (EQA) of labs will help to ensure consistent testing quality throughout Europe and allow comparison between approaches.**
  - This means promoting international platforms for EQA of labs and research into quality (e.g. IQN Path) to improve diagnostics testing and make EQA participation mandatory for labs across the EU.
  - This should also promote consequences for poor performance of labs, e.g. report to a supervisory authority.

- **Tackling delays to reimbursement of new treatments will ensure more systematic and equitable access. This can be improved by:**
  - Supporting better alignment of data requirements between regulators and health technology assessment (HTA) bodies – this would improve evidence development and facilitate the value assessment process
  - Sharing best practices on HTA methodology for PM
  - Developing a more flexible approach that incorporates new technologies (e.g. NGS)
  - Being pragmatic in using the available evidence.
  - Introducing Interim/early access programmes

Report and slides are available HERE

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Investigational Use of Biomarker Tests

Risk-based Approach for Biomarker Assay Deployment in Clinical Trials as an Alternative to CE Marking

- Disparate landscape of regulatory requirements for early phase PM clinical trials
- Often CE mark required for early phase development, not just commercialization of the final test

Represents a significant hurdle to clinical development in the EU

- Proposal to implement a more appropriate, risk-based approach instead
  - Creation of data packages consistent with the context of the clinical investigation

Risk-based Approach for Biomarker Assay Deployment in Clinical Trials as an Alternative to CE Marking

- **Validation of assay in early drug development shall follow the concept of "fit-for-purpose":**
  - Fit: Biomarker assay must be reliable and produce reproducible and accurate data
  - Purpose: Biomarker assay must be suitable for the specified intended purpose

- **Fit-for-purpose is a strategy which allows for continuous and evolving validation process of biomarker assays in course of drug development**

- **Where assays deployed in early clinical trials (even selection assays) pose a low risk to trial subjects a technical validation based on fit-for-purpose approaches is sufficient**
  - Performance of fit-for purpose validation shall follow international/harmonized standards (i.e. CLSI, NCCLS etc.)
  - Results of assay validation shall be well documented and archived
  - Depending on the intended purpose different validation levels are applied (see next slide)
  - Notion mentioned in "EMA Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle"* EMA/CHMP/800914/2016

Minimal Analytical Validation Criteria for a Prototype Assay Following the Proposed Risk-based Approach

	Biomarker Assay in/for early clinical trials		For reference Commercialised assay
Context of Use	Exploratory (including retrospective; not for patient selection)	Selection or Enrichment E.g. BRAF	Commercial / EU
Typically used in Study Phase	I, II	I, II, III	
Sample Types	Contrived samples, spike-ins acceptable	Clinical samples matching tissue/disease type	Clinical samples matching target population
Range/Sensitivity	(✓)	✓	✓
Specificity	(✓)	✓	✓
Robustness	--	(✓)	✓
Stability - Sample/specimen	✓	(✓)	✓
Stability – Reagent	-- /(✓)	(✓) within period of trial	✓
Stability - Onboard (for use on instruments)	-- /(✓)	(✓) preliminary	✓
Shipping stability	--	(✓) within context of trial	✓
Accuracy (results from trueness and precision)	✓	✓	✓
Repeatability	✓	✓	✓
Reproducibility	-- /(✓)	(✓) within context of trial	✓
Cut-off	--	✓	✓
Interferences	--	(✓) within context of specimen & technology	✓
Cross reactions	-- /(✓)	(✓) within context of specimen & technology	✓
Clinical performance	--	--	✓
Scientific validity	--	Scientific rationale	✓

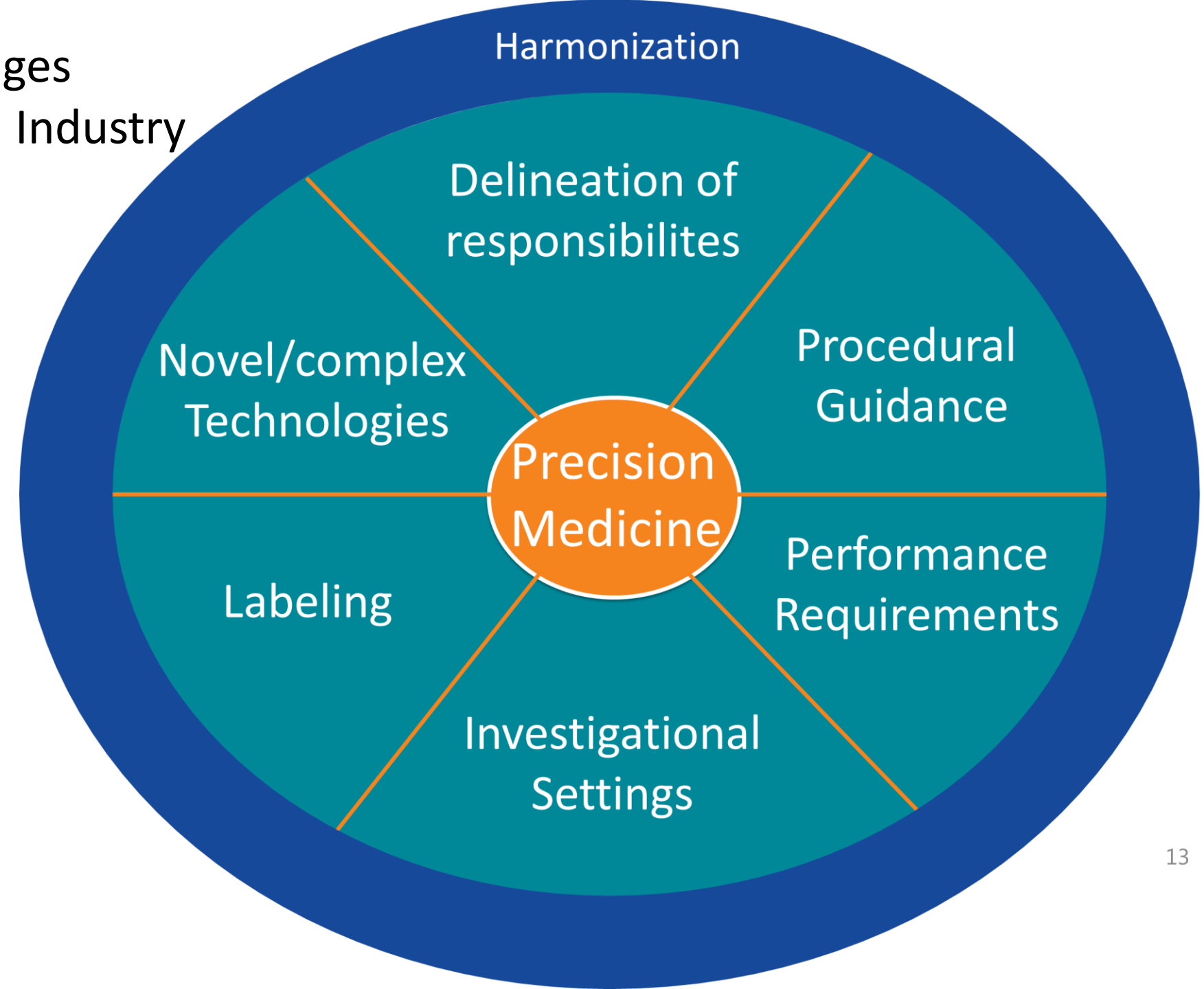
Introduction of the IVD Regulation

EU Regulatory Landscape For Companion Diagnostics

Introduction of the IVD Regulation

- **Previously, regulation of therapeutics and *In vitro* testing elements was decoupled**
- **The IVD Regulation defines companion diagnostics and established regulatory requirements and processes that are linked to therapeutics development**
- **Currently in transition phase with considerable uncertainty**

Key Challenges For Pharma Industry



Challenges Impact Every Aspect Of Assay Development

- **Performance evaluation**
  - Performance Requirements
  - Investigational Use
- **Regulatory Procedures**
  - Delineation of Responsibilities
  - Procedural Guidance
- **Specific Concerns**
  - Harmonized Terminology
  - Labeling
  - Use of novel technologies: NGS

- General advice and principles in scientific and regulatory decision making
- Details on required performance evaluation for different patient risk categories
  E.g. observational screening vs. patient selection

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CE marking : Should not be required for early codevelopment programs
Regulatory requirements should be in line with the investigational test's intented use
Use of prototype clinical trial assays in early therapeutic product trials

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- Procedural guidances are needed
- Process for interaction between EMA/ National Competent Authorities and NBs as well as timing of the various assessments should be defined in a separate procedural guideline

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Process for interaction between EMA/ National Competent Authorities and NBs as well as timing of the various assessments:

- Joined EMA/NB advice during development
- Health Technology Assessment bodies
- Process for information sharing with EMA/NCAs
- Risk Management Plan,
- Resolution of conflict in case of misalignments between NBs and EMA/NCA
- Conditional/ accelerated approval scenarios
- Possibility of approval of a therapeutic product without an approved CE marked CDx

Challenges Impact Every Aspect Of Assay Development

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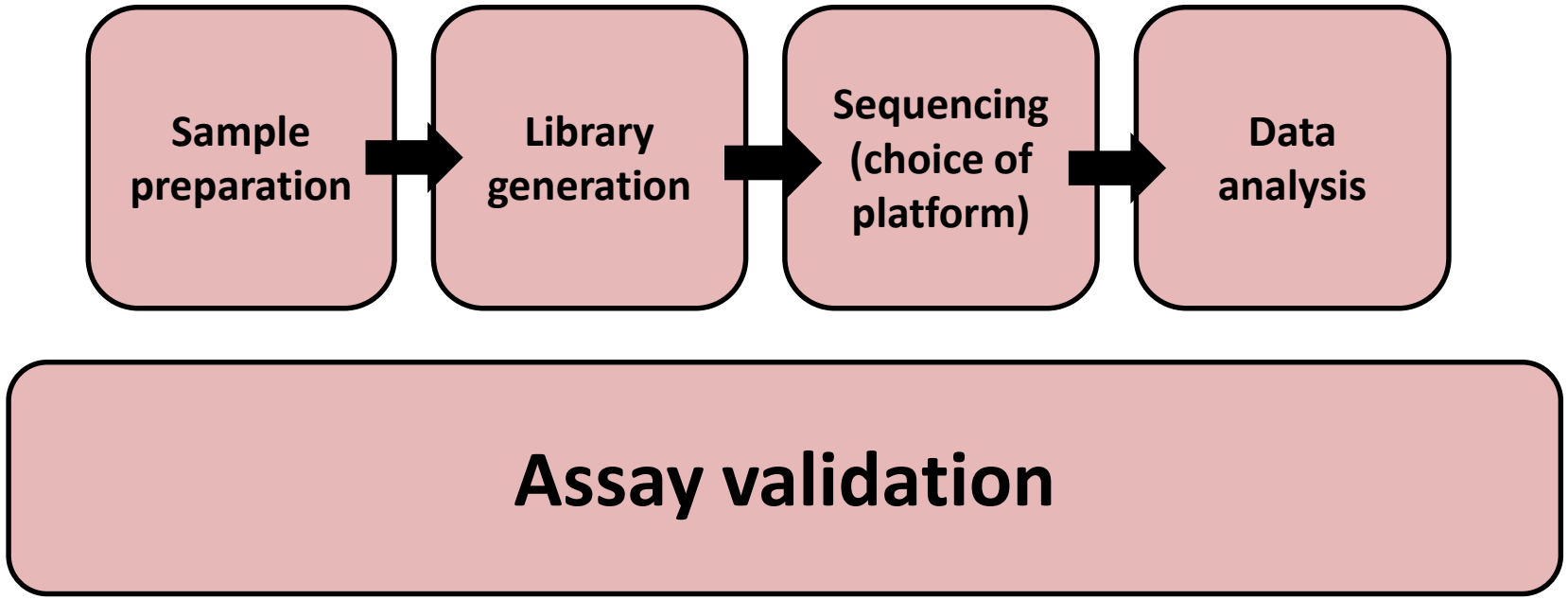
Example of Novel Technology: Next Generation Sequencing

Novel/Complex Technologies: Next Generation Sequencing (NGS)

- **NGS has revolutionized genomic research**
  - Complex, rapidly changing technology with the ability to detect a vast number of disease causing genetic alterations simultaneously
- **Comprehensive genomic profiling will be used as CDx in determining therapeutic treatment of patients**
- **In depth technical review, followed by resulting regulatory challenges associated with NGS, and data protection and storage issues**

Technical Aspects



Regulatory Challenges Associated with NGS & Recommendations

Challenges:

- Setting of performance goals: Uniformity not appropriate
- Differentiation between somatic vs. germline mutation testing
- Lack of standardization
- Transparency in labeling
- Rapidly changing hardware and software
- Uncertain evidence requirements for investigational settings

Recommendations:

- Performance metrics should be consistent with the context of use
- Common performance goals should not be established
- Need for global reference materials with known performance characteristics
- Need for labeling with transparency on limitations and performance characteristics
- Develop best practices for change management
- Clear regulatory guidance needed on appropriate validation requirements

Data Protection and Data Storage

Analysis and recommendations for:

- Coding schemes to protect privacy
- Informed consent
- Transparency in communication of NGS results
- Storage of and access to NGS data and samples

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