CE Marking of Clinical Trial Assays

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Almac Diagnostics

Almac Diagnostics is a global precision medicine company, Providing:

- **Discovery**
- **Development**
- **Commercialisation**

of complex diagnostic and companion diagnostic tests.

Overview

- Why are EU regulators asking for CE marking of certain clinical trial assays (CTAs)?
- Biomarker Assay Use and CE Marking
- Examples of Clinical Trial Assay use and when CE marking is required
- Tasks for CE marking during CDx development
- Aligning with USA clinical trial (IDE) regulations (Almac Diagnostics single site CE mark perspective)
- Important Considerations/Nuances
- Summary

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Why are EU regulators asking for CE marking of certain (CTAs)?

Aligns with the EU Regulators developing views of Biomarkers
Quote from latest concept paper:

"The potential to align technical assay validation and clinical evidence requirements for drug approval with technical and clinical performance requirements for CE marking will be discussed."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/641298/2008
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development
9 June 2011
EMA/446337/2011
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection
28 April 2016
EMA/CHMP/268544/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on good pharmacogenomic practice

20 July 2017
EMA/CHMP/800914/2016
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle

Why are EU regulators asking for CE marking of Certain (CTAs)?

Technical Performance requirements of assays used to measure predictive Biomarkers depend on:

- **Stage of development** (early vs pivotal study)
- Whether **Biomarker status** affects study entry
- **Subject eligibility** and **treatment allocation**
- **Timing of the assay development** in relation to drug development
- **Use of central laboratory testing** (complex tests)

20 July 2017
EMA/CHMP/800914/2016
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle

It is anticipated that the **draft guideline will be available 9-12 months after the end of the public consultation of the concept paper** (August-November 2018) and will be released for 6 months external consultation.

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Biomarker CTA Use and CE Marking

Research Use Only

Biomarker research not for clinical use or patient stratification

CE mark not required

Assay confirmed by CE marked test

Assay results not used during trial
Not for Patient Management

CE mark or Performance Evaluation

Inclusion / exclusion
Drug or placebo
Dose A or Dose B

For Patient Management

CE Mark Required

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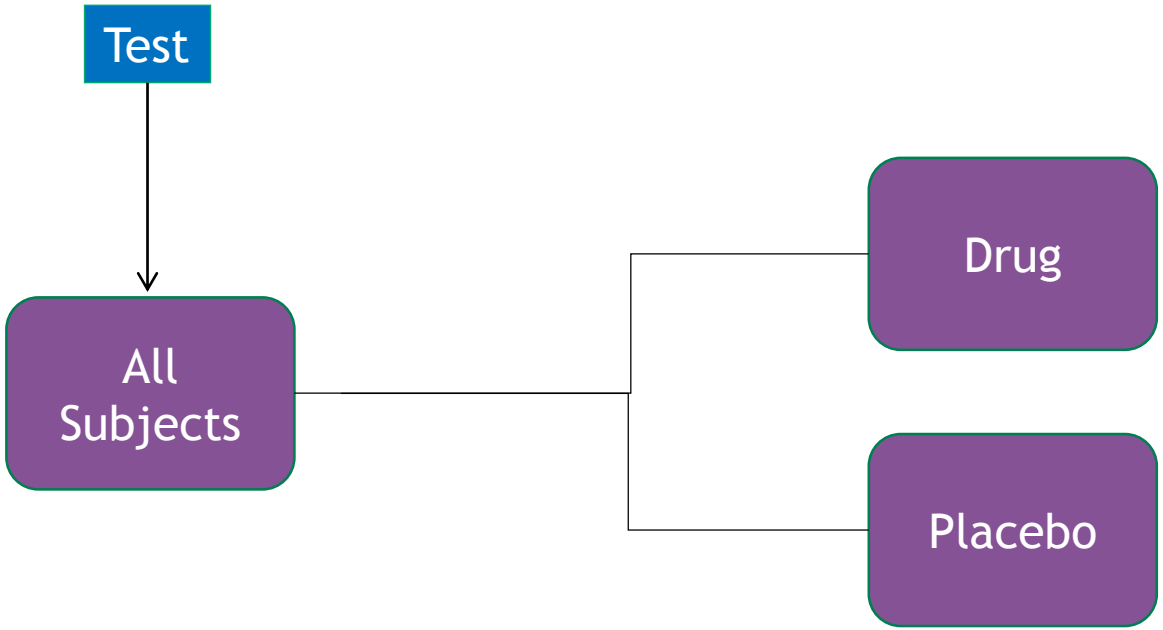
Clinical Study Designs- Test Usage is Exploratory Only



- Interaction analysis between treatment & test
- Test is not used as randomisation criterion
- Does not provide full validation of the test

The role of the assay is exploratory only i.e. **RUO use and CE marking is not necessary**

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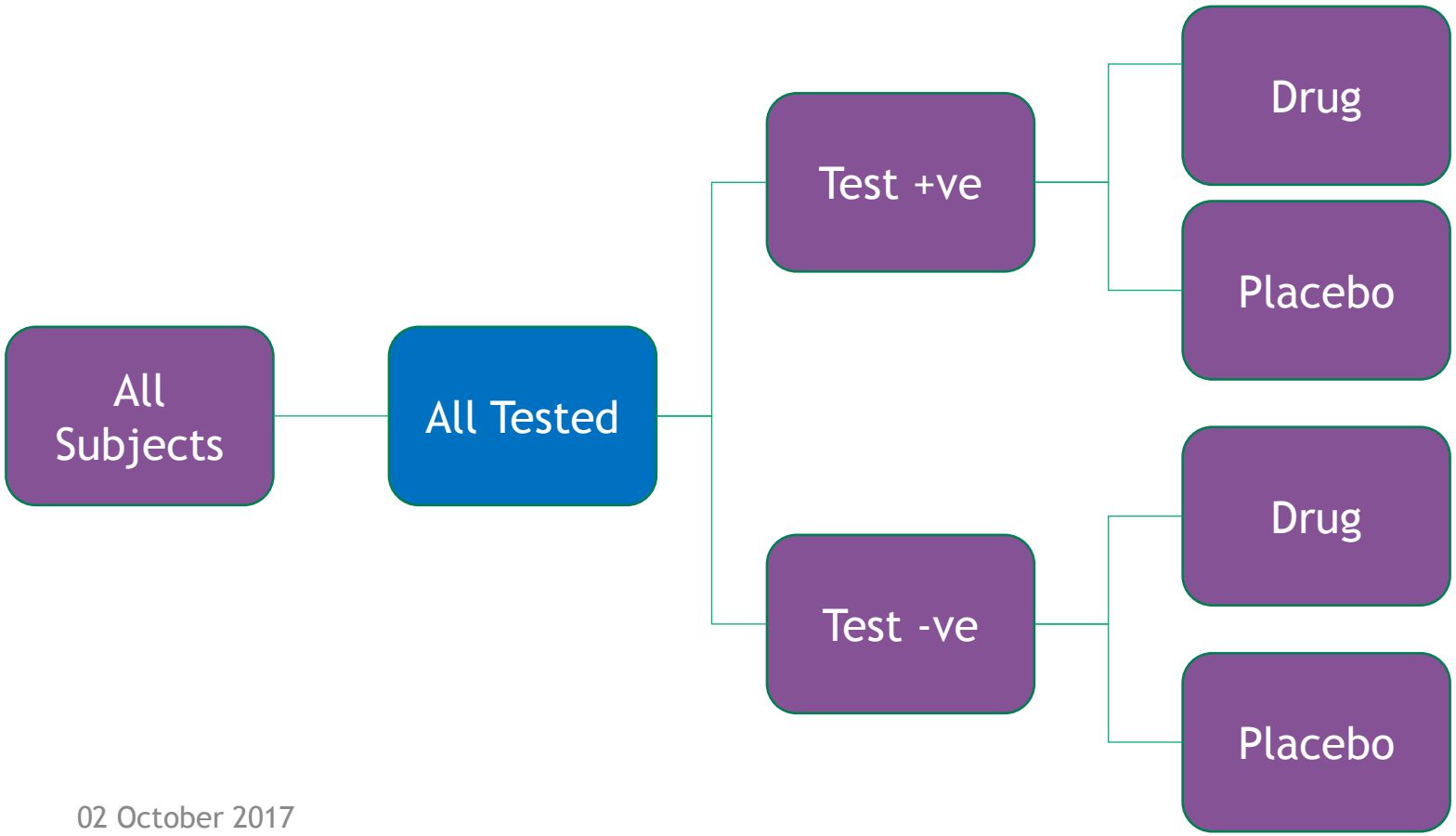
Clinical Study Designs-Randomised Trial Design



Test is utilised for informing randomisation:

- Prior info on performance of the test may not be necessary
- Good trial design to validate both assay and drug

CE mark will be the consequence of this i.e. a Performance Evaluation Registration will be required

Prior CE mark of CTA is not essential as the test is not selecting Drug v placebo

Biomarker CTA use and CE Marking

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CE mark not required

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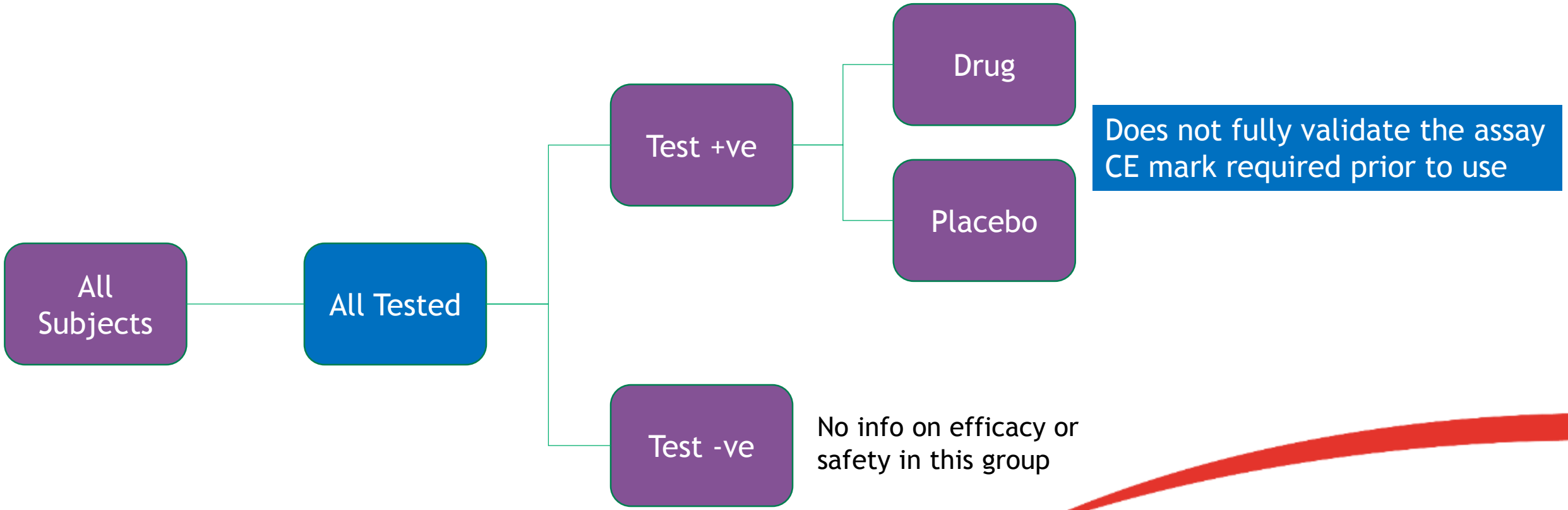
Clinical Study Designs-Targeted trial Design

Drug use integrally linked with use of the test at the time of approval:

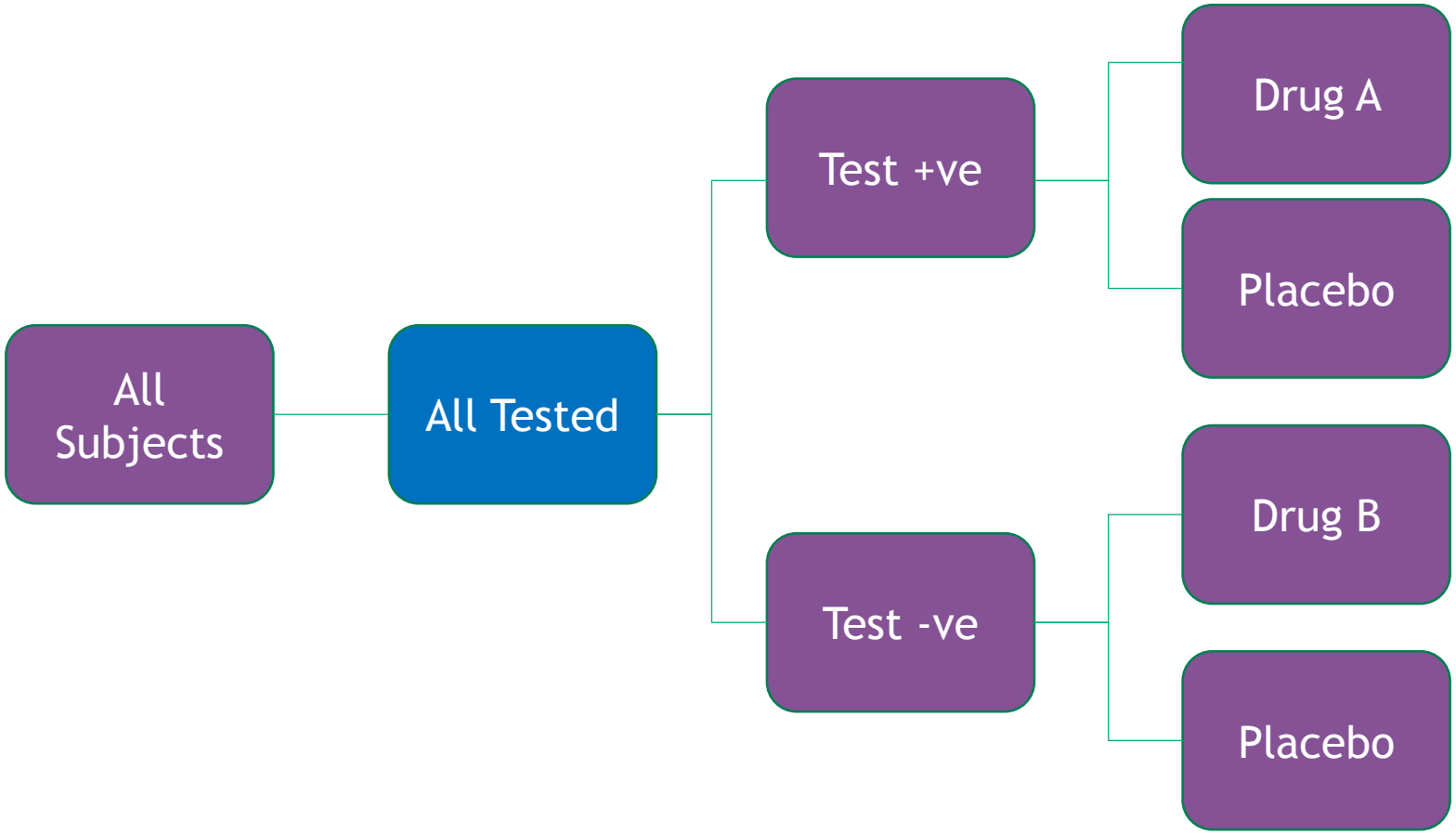
- Prior info on performance of the test crucial
- Useful when biological evidence linking the marker and disease state is certain



Clinical Study Designs-Drugs A and B are different

Test is utilised for informing randomisation:

- Prior info on analytical performance of the test is necessary



CE mark is required if Drugs A and B are different

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Tasks for CE marking during CDx Development

So how do clinical laboratories utilising CTA's in support of these trials comply?

Advice from MHRA:

"At the time of the clinical trial application, the CE mark need only be for the analytical performance of the IVD (eg detection of a biomarker) and will include reagents, equipment, calibrators, controls and software. These are likely to be self certified IVDs."

But for Self certification you still require a Technical File….

- Quality System
- Design information
- Product operation
- Risk analysis
- Performance evaluation
- Labelling and IFU
- Stability
- Post Market Surveillance

For CE Marking of a CTA

The scale of the technical file is limited by the Intended Use of the Assay in the trial

- Intended Use for the assay is specific to the trial use not commercial use
- Performance claims are for analytical parameters only not clinical
- Limiting the scope of the CE mark to a single testing site essentially means aligning the testing laboratories Quality System, usually **ISO15189** (EU) or **CAP/CLIA** (USA), with IVD manufacturing Quality System e.g. **ISO13485**.

Technical File for single site CTA CE mark

- Quality System- ISO15189/CAP/ISO13485
- Design information- specific to CTA
- Product operation- specific to CTA use
- Risk analysis- specific to trial subject risk
- Performance evaluation-analytical only
- Labelling and IFU
- Stability- Trial orientated
- Post Market Surveillance- Monitoring

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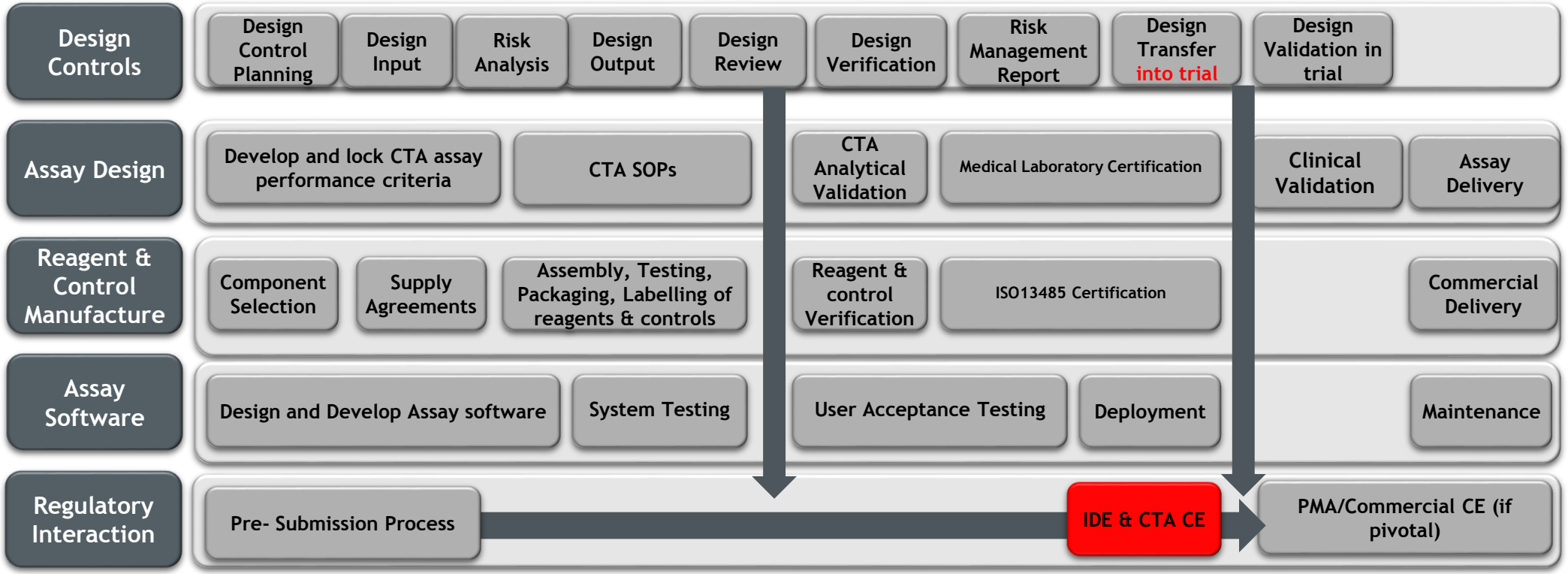
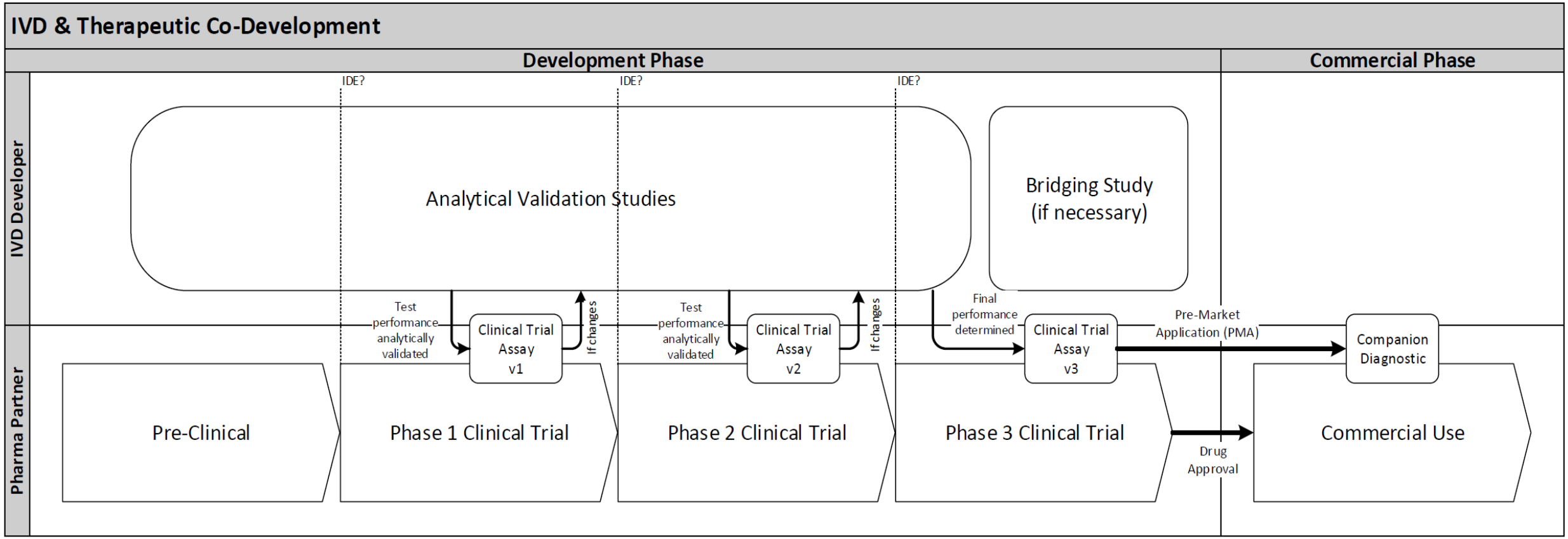
Essentially CTA CE ark ≈ US IDE Requirements

Almac Diagnostics Approach:



The Development Pathway may require several CTA CE Marked Assays



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Important Considerations /On the Horizon

(1) **Always check with each Competent Authority (CA) prior to site initiation**

Site of Assay testing can be important:

- Some CA e.g. MHRA don't require CE marking if the testing site is outside of EU but others do

Even if you CE mark a CTA you may also need to register for performance evaluation:

- If the trial is a pivotal trial

(2) **The EU IVDR is in transition and Annex XIV will apply for Interventional PE studies**

(3) **New EU guidance on Biomarker/ Drug Co-Development is pending**

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Summary

- **EMA looking at the use of biomarker assays in therapeutic product trials to ensure that:**
  - There are no patient safety issues linked with use if the assay
  - Trial endpoints aren't jeopardised by assay use

- **CE marking of CTA's may be required depending on:**
  - Specific EU trial sites and Competent Authority involved in the trial
  - Location of the testing laboratory
  - Use of the assay in the trial

- **New guidance's and the IVDR are imminent which will inform this area.**

Questions?

Thank You

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