In Vitro Diagnostic assay for genotyping of clinical study participants

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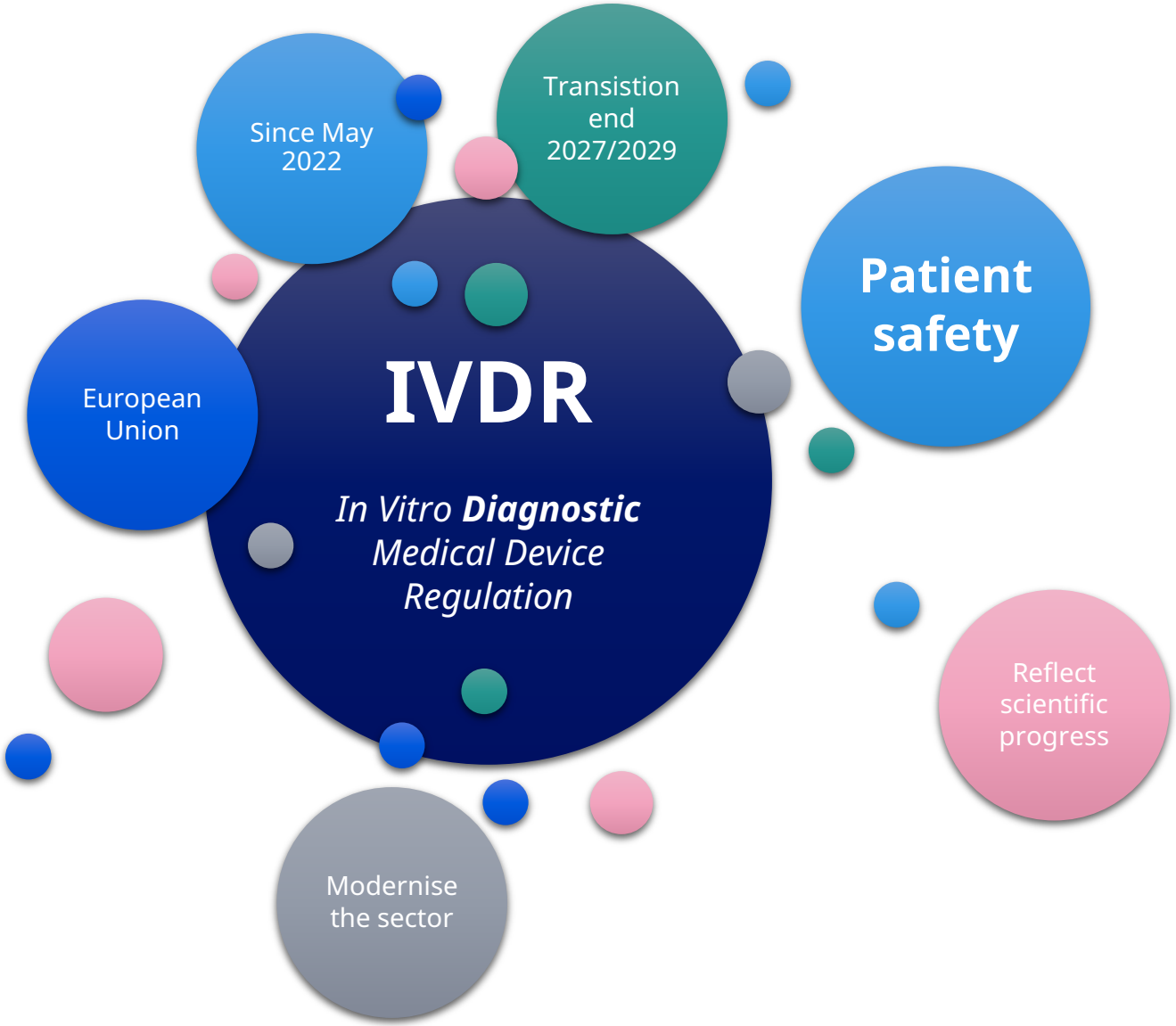
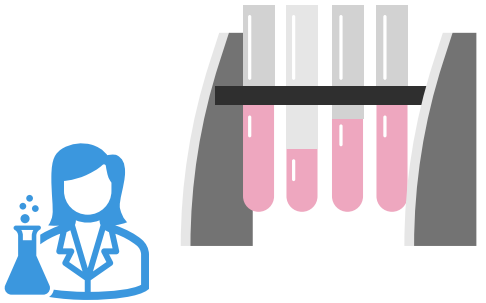
IVDR – an EU regulation



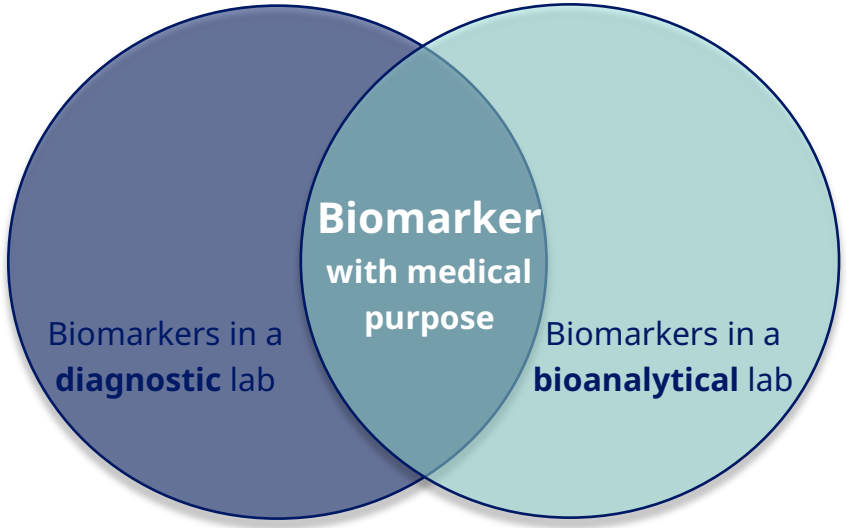
In vitro diagnostics – Is it important for me?

- IVDR world of diagnostic labs, safety and central laboratories
- ”Not relevant” for me as *analyical biomarker scientist* in the clinical trial



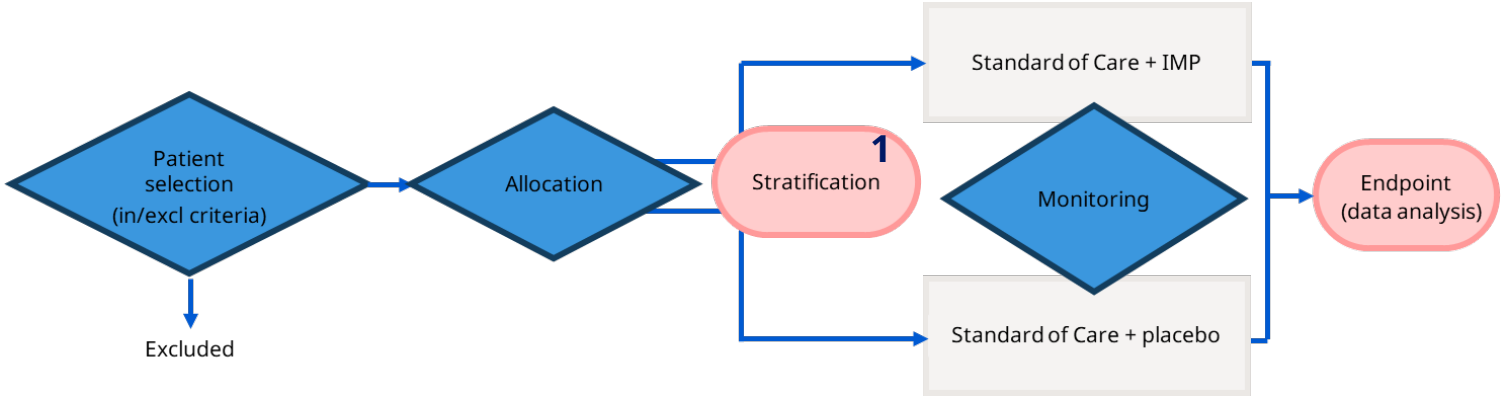
……. But

- Use of biomarkers constantly changes with development of clinical trial design
  - Some biomarkers used solely as clinical endpoint
  - Biomarkers move from explorative to decision making and may be assigned a **medical purpose** in a trial



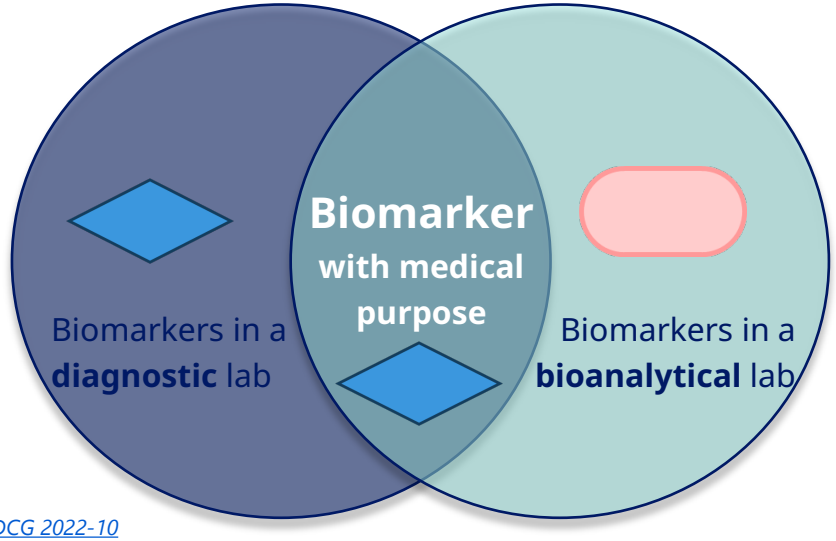
- Important to understand IVDR to ensure **only assays in scope are put in scope**

When is a biomarker in scope of IVDR?



IVDR likely required, as used for medical management decisions

IVDR **NOT** required, as likely no impact on medical decision



Guidance - MDCG endorsed documents and other guidance (europa.eu) : Medical Device Coordination Group Document MDCG 2022-10

1: In the US, stratification is also mentioned as an example of patient management, which could trigger requirements for Investigational Device Exemption

Case: A genotyping assay in-scope of IVDR

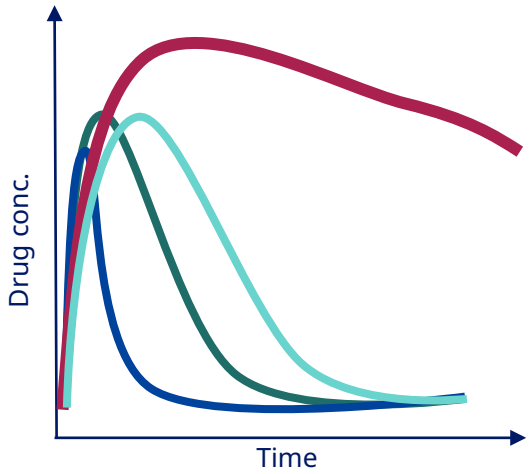
CASE

Risk of prolonged and increased exposure

Compound: Small molecule

Metabolism: Cytochrome P450 2D6 (CYP2D6) responsible for drug metabolism has several genotypes, which affect metabolite rate of drug.

- **Ultra rapid**, **Normal**, **Intermediate**, and **poor** metaboliser
- **Poor metaboliser** predicted to have prolonged and increased exposure

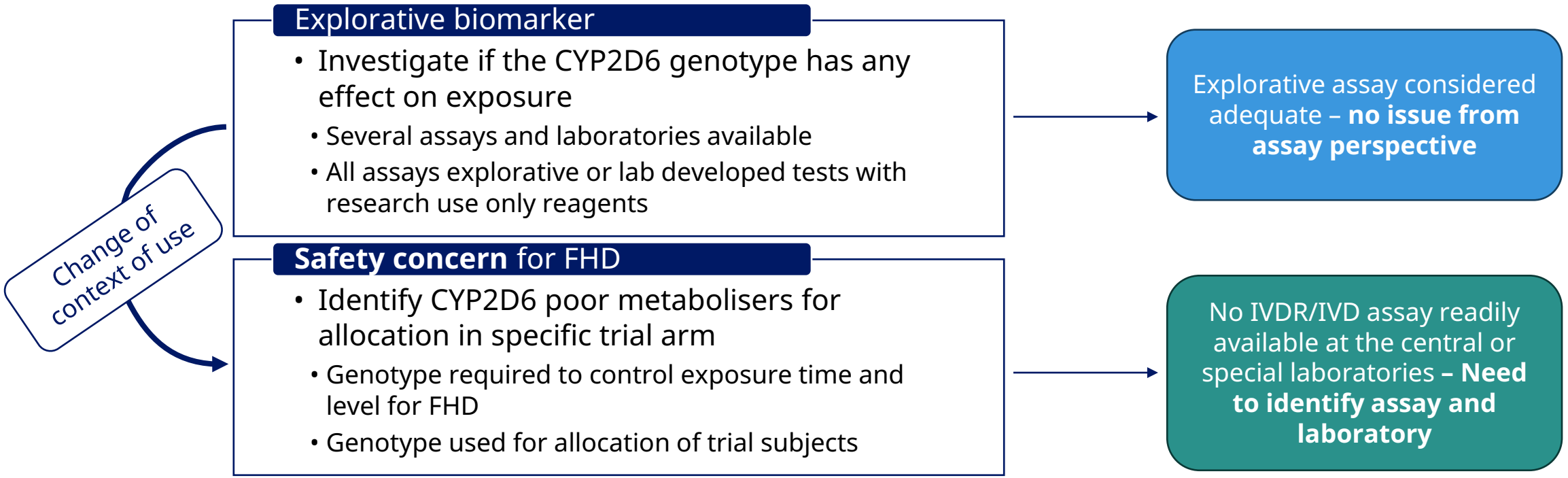


Biomarker: CYP2D6 genotype

Graph for illustrative purposes only

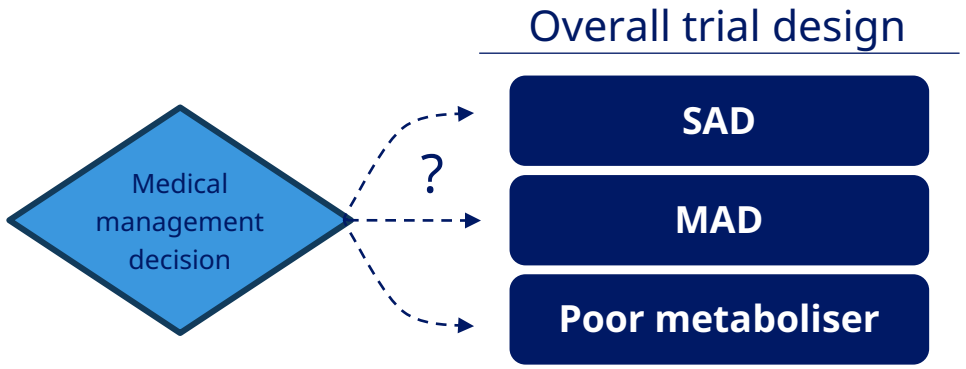
CASE

Context of use changed for the project

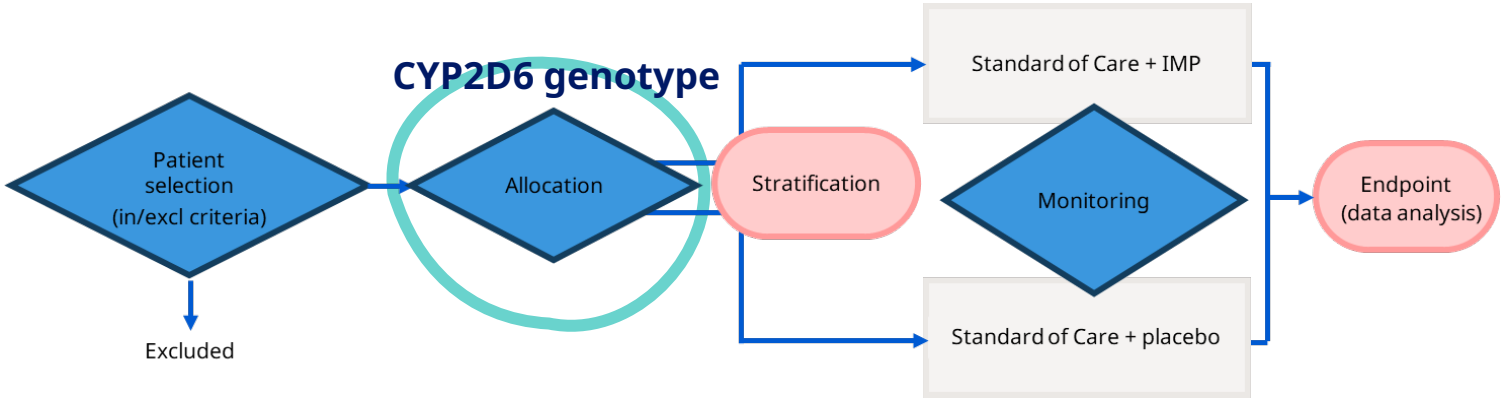


CASE

Why was an IVDR assay required?



- Results will be used to allocate poor metabolisers to a specific arm in the trial.
  - IVDR assay is requried.
- Authorities commented the assay should have the relevant mark of conformity



CASE

IVDR – also an effect for UK trials

- UK not part of EU, thus not regulated by IVDR
- Slightly different timing, but IVDR-like regulation expected in UK Q2 2025[1]

- For this case the timelines for trial enabled us to continue with CE IVDD certified assay:

  - **Our requirements: CE IVDD assay and ISO15189 lab**

1 *Transition periods under new UK SI (publishing.service.gov.uk)*

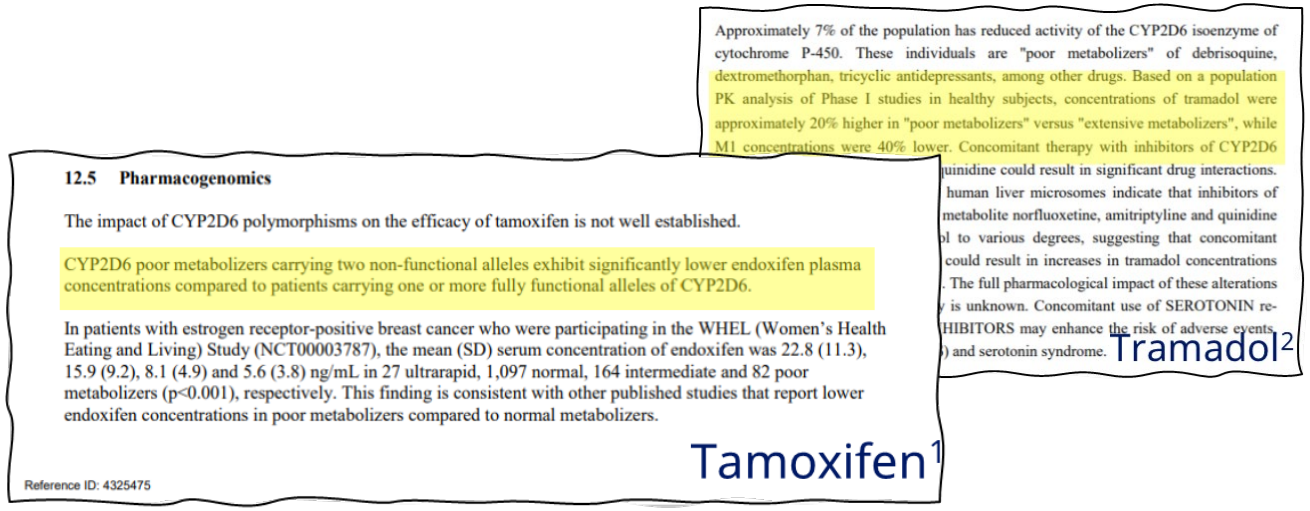
CASE

Several marketed drugs are metabolized by CYP2D6

It is well known that metabolism of some small molecule drugs is depending on CYP2D6 genotype

- Examples of marketed drugs:
  - Tamoxifen, several antidepressants, Tramadol etc.
- CYP2D6 genotyping may be used for regulating doses of some of the marketed drugs[3]

→ There must be an IVD(R) assay available



12.5 Pharmacogenomics

The impact of CYP2D6 polymorphisms on the efficacy of tamoxifen is not well established.

CYP2D6 poor metabolizers carrying two non-functional alleles exhibit significantly lower endoxifen plasma concentrations compared to patients carrying one or more fully functional alleles of CYP2D6.

In patients with estrogen receptor-positive breast cancer who were participating in the WHEL (Women's Health Eating and Living) Study (NCT00003787), the mean (SD) serum concentration of endoxifen was 22.8 (11.3), 15.9 (9.2), 8.1 (4.9) and 5.6 (3.8) ng/mL in 27 ultrarapid, 1,097 normal, 164 intermediate and 82 poor metabolizers ($p<0.001$), respectively. This finding is consistent with other published studies that report lower endoxifen concentrations in poor metabolizers compared to normal metabolizers.

Reference ID: 4325475

Tamoxifen[1]

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 quinidine could result in significant drug interactions. human liver microsomes indicate that inhibitors of metabolite norfluoxetine, amitriptyline and quinidine ol to various degrees, suggesting that concomitant could result in increases in tramadol concentrations. The full pharmacological impact of these alterations is unknown. Concomitant use of SEROTONIN re-HIBITORS may enhance the risk of adverse events,) and serotonin syndrome.

Tramadol[2]

1:SOLTAMOX® (Tamoxifen citrate) oral Full Prescribing Information, 2:ULTRAM®, (tramadol hydrochloride) Tablets Full Prescribing Information, 3: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

CASE

Identifying an assay and suitable laboratory

No IVDR/IVD assay available at our central or special laboratories – **Needed to identify assay *and* laboratory**

If not successful, the trial would be delayed

Identify kit

- Search for existing assay with IVDD certification

Identify lab using kit

- Contacted manufacturer for identification of laboratories running their assay

Ensure relevant certification

- The lab had to be ISO15189 certified

Assess laboratory

- Internal assessment of laboratory

CASE

Final selection of laboratory

Idenfitied a ISO15189 Clinical diagnostic laboratory with CE IVDD assay running

- Acceptable assay and performance
- Acceptable archiving
- Acceptable quality management system etc.

Several operational challenges

- Not used to working with big pharma/clinical trials
- Good Clinical Practise training required
- Instructions not in English

CASE

Summary – CYP2D6 genotyping for subject allocation

1

The CYP2D6 biomarker was considered in scope of IVDR

- Used for allocation of study subjects

2

Because study was run in UK, CE IVDD, would be acceptable

3

Existing assays were all explorative

4

Successfully identified an IVDD assay and ISO15189 laboratory

- Significant risk for delay of the trial

Thank you for listening

Questions?

Image generated with Azure Dall-E