



New Translational Biomarkers for Drug Induced Organ Injury - The IMI SAFE-T Project

*Safer And Faster Evidence-based Translation

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Outline

- Background
- SAFE-T objectives
- Structure and deliverables
- Biomarker qualification process
- Achievements
- Challenges
- Next steps



SAFE-T: because safety matters...

Between the **years 1900 and 2000**,
average life expectancy has increased from
45 to 77 years of age

 Part of this is due to innovative medicines

**Lazarou J et al. (1998) JAMA ; 279(15):1200-1205*



SAFE-T: because safety matters...

- However, making medicines safer is still one of the key challenges in pharmaceutical development
 - In the US, fatal Adverse Drug Reactions (ADRs) are the 4th to 6th leading cause of death*
 - Incidence has been stable for more than 30 years*
 - Costs directly attributable to ADRs may lead to an additional \$1.56 to \$4 billion in direct hospital costs per year in the US*

**Lazarou J et al. (1998) JAMA ; 279(15):1200-1205*



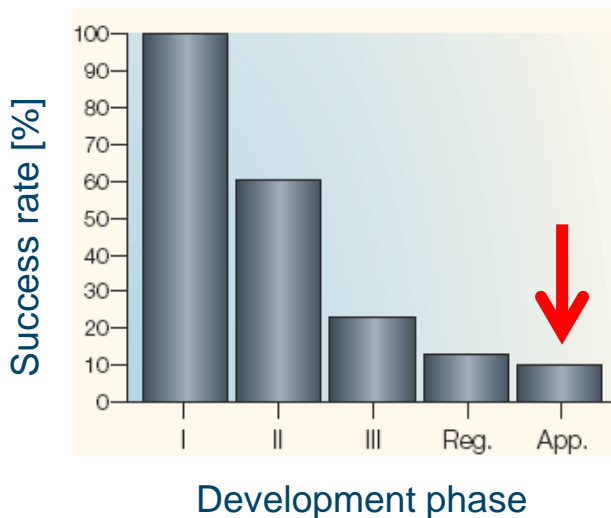
SAFE-T: because safety matters...

- For many serious drug side effects, tools are lacking for adequate
 - prediction
 - detection
 - monitoring

- This is particularly the case for drug induced injury to the
 - kidney
 - liver
 - vascular system

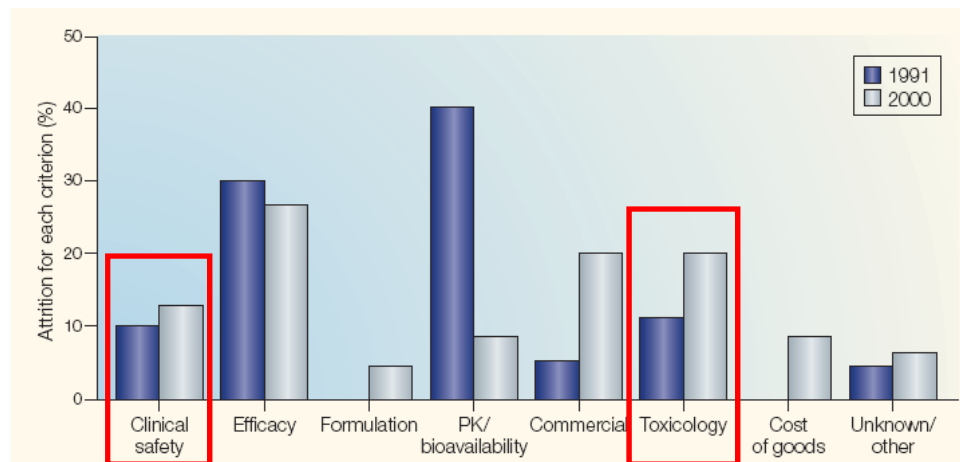
Drug safety: room for improvement

The economic perspective



- Around 90% of compounds entering clinical development fail

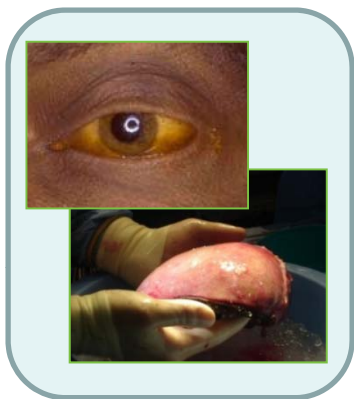
- 30% of these failures are due to clinical safety and toxicology



Kola et al. (2004), Nat Rev Drug Discovery ; 3: 711-15

Drug safety: need for improvement

The patient perspective



Drug induced liver injury (DILI)
Worst cases transplantation, death



Drug induced kidney injury (DIKI)
Worst cases hemodialysis, transplantation, death



Drug induced vascular injury (DIVI)
Worst cases multi-organ failure, death



IMI SAFE-T Consortium

Objectives

- To **evaluate utility** of safety biomarkers for detecting, assessing, and monitoring drug induced kidney, liver, and vascular injury **in humans**.
- To **develop assays** and devices for clinical application of safety biomarkers
- To compile enough evidence to qualify safety biomarkers for **regulatory decision making in clinical drug development** and in a **translational context**
- To gain evidence for how safety biomarkers may also be used in the **diagnosis of diseases** and in clinical practice

Biomarker attributes of interest

- Patient level
 - Lower injury threshold
 - Earlier time to onset
 - Larger extent of changes
 - Improved specificity
 - Better suited to monitor and predict clinical course
 - Better suited to assess causality

- Population level
 - Earlier and more specific signal detection in clinical development programs
 - Improved mechanistic insight
 - Superior in terms of identifying underlying pathology
 - Better suited to predict human risk from animal toxicity

Key challenges for biomarker qualification

- Substantial background variability in initial candidate markers
 - Biomarker response varies across different populations
 - Large initial number of biomarker candidates requires substantial sample volumes to be taken
 - Key target responses, i.e. specific adverse drug reactions, suitable and accessible for qualification are overall very rare
- Large sample sizes are required
 - Multitude of patient populations need to be included

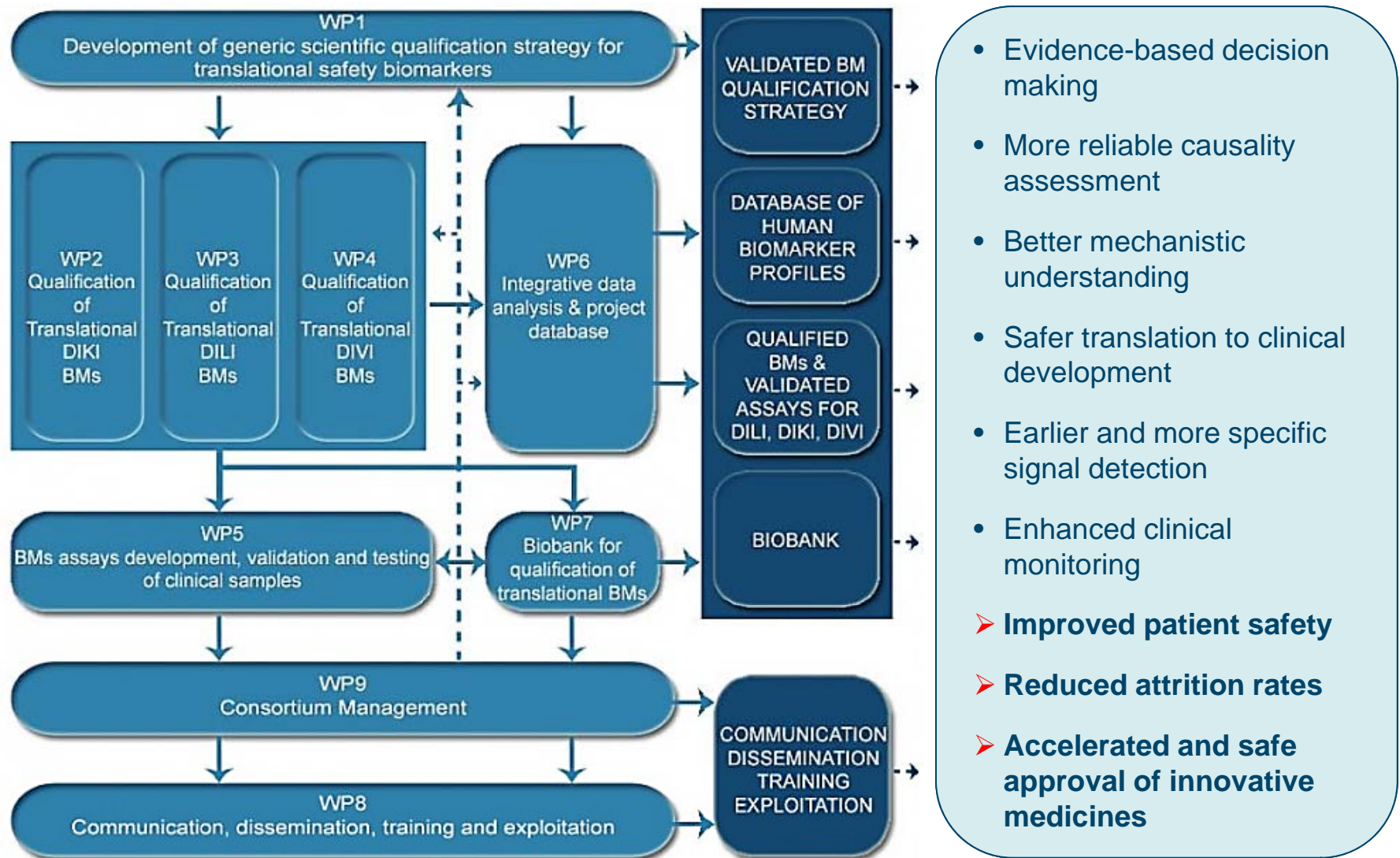
 **Qualification cannot be achieved by one company alone**

SAFE-T participants





SAFE-T structure and deliverables



Funding and timing

Financing

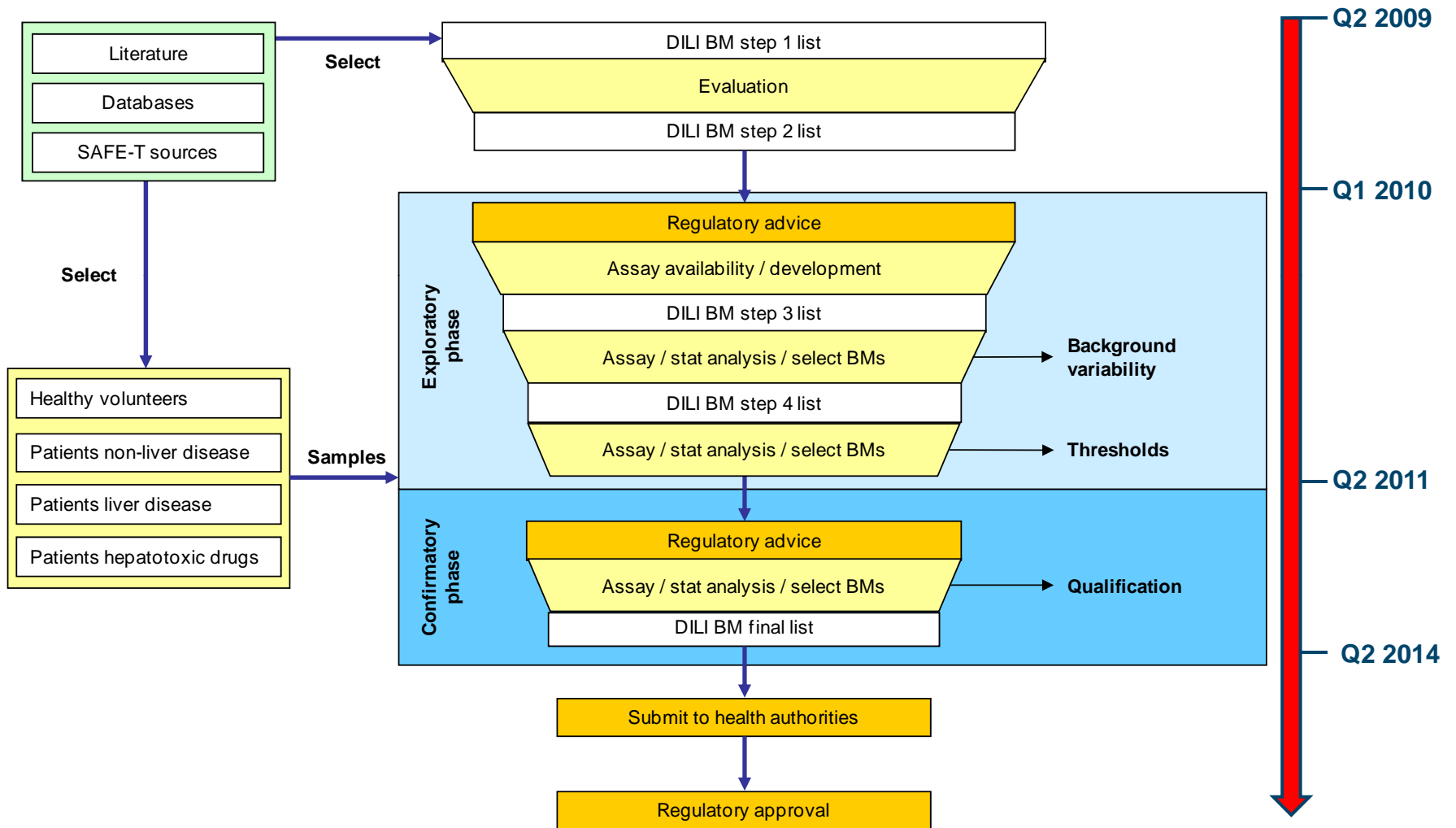
- IMI funding: 13.9 mio EUR
- EFPIA contribution, mainly in kind: 17.7 mio EUR
- Contribution academia/SME: 4.1 mio EUR
- Total project cost: 35.7 mio EUR

Timing:

- Starting date: June 15, 2009
- Duration: 5 years

Biomarker qualification process

Elements and process flow



DILI biomarker candidates selected for qualification

Serum or Plasma Marker	Assays	Liver specificity	Human data	Pathology	
albumin mRNA	RT-PCR	highly specific	yes	hepatocellular damage	
Microglobulin precursor (Ambp) mRNA	RT-PCR	highly specific	yes	hepatocellular damage	
Conjugated/unconjugated bile acids	LC-MS	highly specific	only in tissues	hepatocellular damage	
high mobility group box 1 (HMGB1)	LC-MS	not specific	yes	cholestasis	
Cytokeratin 18 (KRT18)		not specific	yes	hepatocellular damage	
ALT 1 & 2	Immuno assays LMX	highly specific	yes	hepatocellular damage	
alpha fetoprotein (AFP)		Specific	yes	hepatocellular damage	
Arginase 1		highly specific	yes	hepatocellular damage	
Colony stimulating factor receptor (CSF1R)		not specific	yes	inflammation	
F-protein (HPPD)		highly specific	yes	hepatocellular damage	
Glutathione S transferase alpha (GSTa)		specific	yes	hepatocellular damage	
Leukocyte cell-derived chemotaxin 2 (LECT2)		not specific	yes	inflammation	
ST6Gal 1		specific	yes	inflammation	
Osteopontin		not specific	yes	inflammation	
Paraoxonase 1 (PON1)		not specific	yes	steatosis	
Prothrombin		not specific	yes	steatosis	
Regucalcin (RGN)		specific	only in tissues	hepatocellular damage	
ALT1/2			highly specific	yes	hepatocellular damage
Glutamate dehydrogenase (GLUD, GLDH)		Enzyme activity	specific	yes	hepatocellular damage
Purine nucleoside phosphorylase (PNP)	activity	specific	no	hepatocellular damage	
Glutathione S transferase alpha (GSTa)		specific	yes	hepatocellular damage	
Malate dehydrogenase (MDH)		not specific	yes	hepatocellular damage	

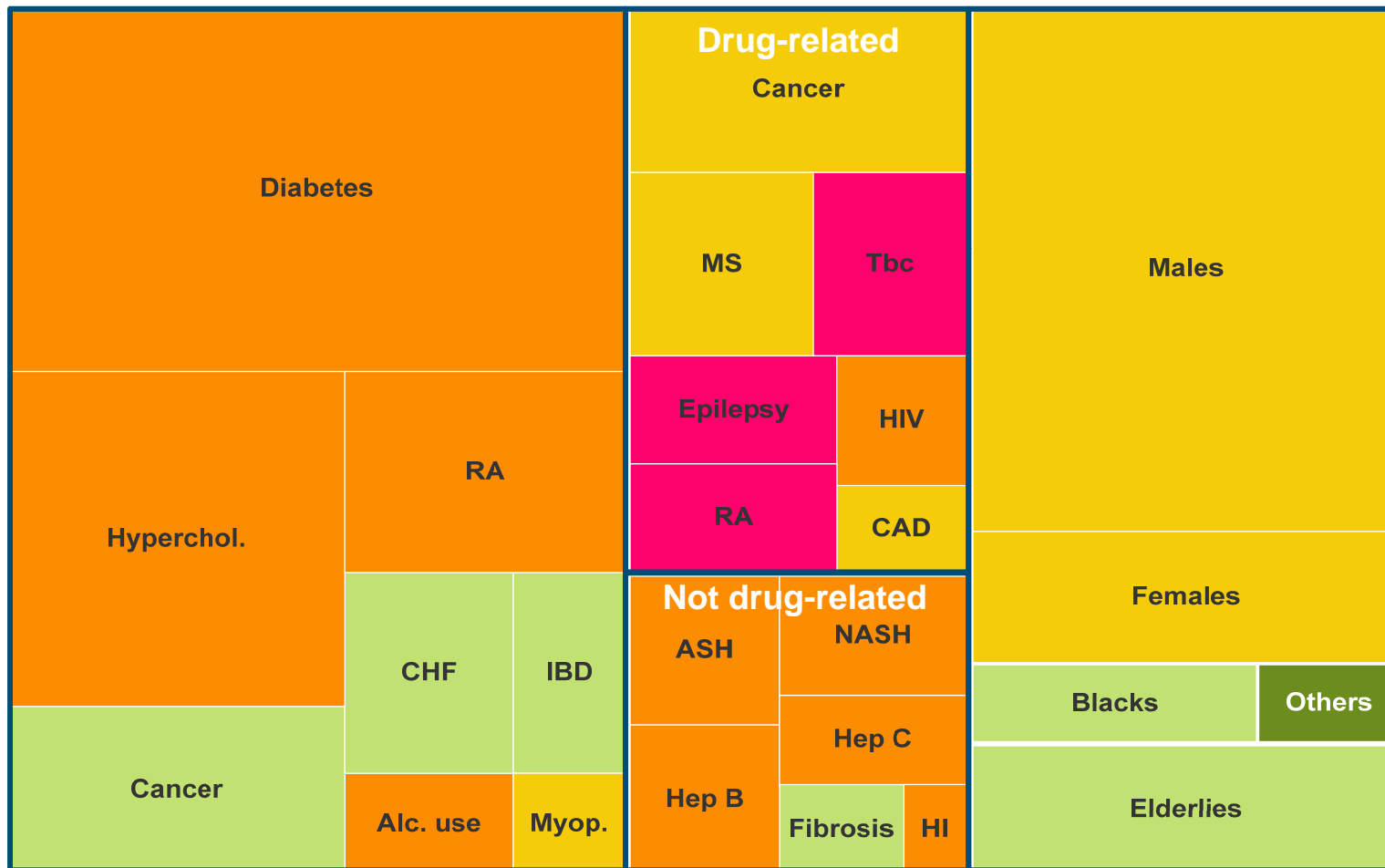
Composite disease markers to be assessed in addition: ActiTest™, Fibrotest™, SteatoTest™

DILI biomarker qualification:

The „population mosaic“



┌
┌
Patients
+
Liver
+
Healthy subjects
└



Color by relevance, area by population size

Relevance: 5 4 3 2 1





SAFE-T achievements

- Generic qualification strategy defined
- Biomarker candidates prioritised, assay development ongoing
- Study protocols for prospective DILI studies submitted for IRB review
- Completed HV study to assess within and between subject variability (Sanofi Aventis) and access to HV samples (AstraZeneca)
- Set up central biobank for sample storage
- Initiated regulatory interactions via briefing meetings with EMA/FDA
- Established collaboration with Predictive Safety Testing Consortium (PSTC)

Key challenges for the consortium

	Gap/Challenge	How addressed?
Biomarker candidates	<ul style="list-style-type: none"> • Out of scope: <ul style="list-style-type: none"> ○ Genetic susceptibility markers ○ Preclinical assay validation ○ Preclinical biomarker discovery 	<ul style="list-style-type: none"> • Covered by SAEC, DILIN, others • Close collaboration with PSTC
	<ul style="list-style-type: none"> • Lack of functional and susceptibility marker candidates 	<ul style="list-style-type: none"> • Biomarker discovery based on human cases from SAFE-T clinical studies, using mass spec and protein antibody array analyses of plasma samples
Methodology	<ul style="list-style-type: none"> • Due to low DILI prevalence, any new marker will have a low PPV. <ul style="list-style-type: none"> ○ Improvement is mainly needed in specificity rather than sensitivity. ○ Added value of new markers may be primarily as part of panels 	<ul style="list-style-type: none"> • Identify suitable marker panels • Use advanced statistical methods such as lasso regression and gradient boosted models
Logistics	<ul style="list-style-type: none"> • Access to DILI cases • Sampling requirements need to be aligned across different SAFE-T working groups • Sampling to be seamlessly integrated into standard clinical trial workflows 	<ul style="list-style-type: none"> • Add two studies in high risk patients • Dedicated cross-work package team to ensure alignment • Provide standard protocol and ICF text sections • Simplify sample collection, processing, and shipment • Use samples available already



SAFE-T: next steps

- Set up consortium database
- Initiate prospective studies
- Include sampling into standard clinical trials
- Finalize agreement with PSTC

Acknowledgements

(Incomplete) SAFE-T participant list, *team leaders*



Neus Prats	Almirall	Katja Matheis	Boehringer Ingelheim	Andrew Nicholls	GSK	Steve Hall	Pfizer
Eric Massana	Almirall	Joachim Stagnier	Boehringer Ingelheim	Elaine A. Irving	GSK	Stefan Sultana	Pfizer
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Thanks for your attention...



...I'm happy to take your questions

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