SAFE-T

Safer And Faster Evidence-based Translation

http://www.imi-safe-t.eu

IMI Stakeholder Forum June 14-15, 2010

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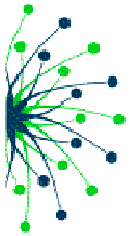
Outline

- Background
- Definitions
- SAFE-T scope and objectives
- Structure and deliverables
- Biomarker qualification process
- Interfaces
- Achievements
- Next steps



Acknowledgements

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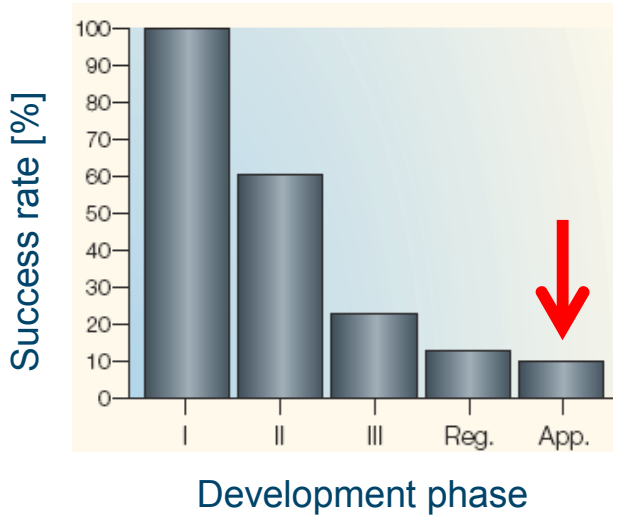
SAFE-T: because safety matters...

- Between 1900 and 2000, average life expectancy has increased from 45 to 77 years of age
  - Part of this is due to innovative medicines
- 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*
  - Fatal ADRs in the US alone are in the range of 100‘000 per year*
  - Costs directly attributable to ADRs may lead to an additional $1.56 to $4 billion in direct hospital costs per year in the US*
- For many serious drug side effects, tools for adequate prediction, detection, and monitoring are lacking
- This is particularly the case for drug induced injury to the kidney, the liver, and the vascular system

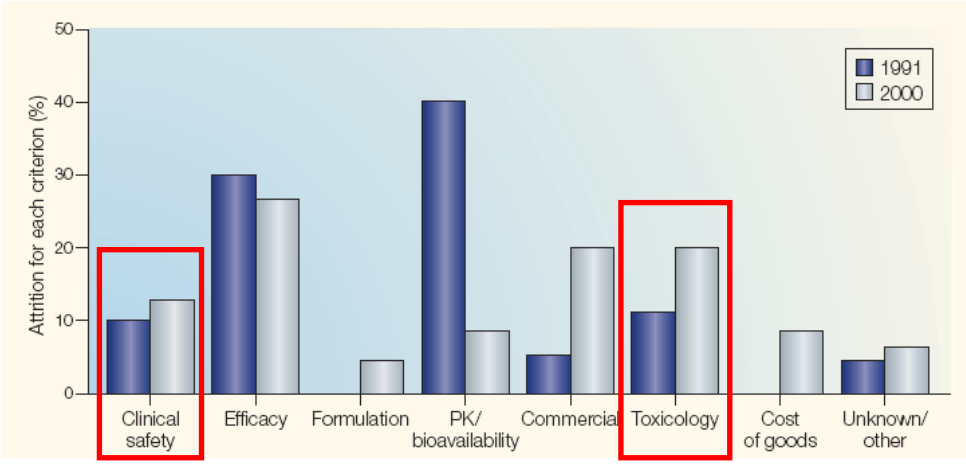
**Lazarou J et al. (1998) JAMA ; 279(15):1200-1205*

Drug safety: room for improvement

The economic perspective



- **Around 90% of compounds entering clinical development fail**

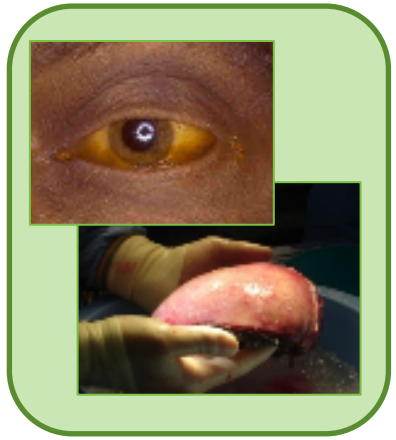


- **30% of these failures are due to clinical safety and toxicology**

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

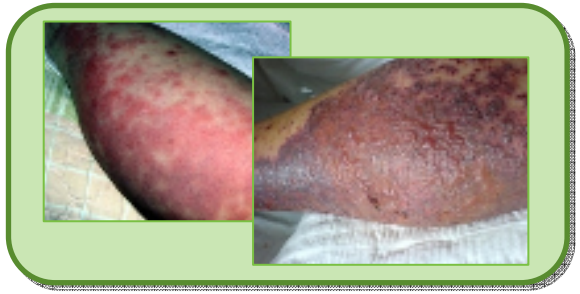
Drug safety: **need** for improvement

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

Some definitions…

- **Clinical endpoint:**

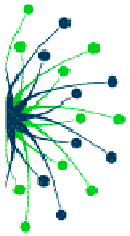
  A characteristic or variable that reflects how a patient feels, functions, or survives.

- **Biological marker (biomarker):**

  A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

- **Surrogate endpoint:**

  A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.



NIH Biomarkers Definitions Working Group (2001). Clin Pharm Ther 69(3): 89-95

…and some more

I Known valid biomarker:

A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results

II Probable valid biomarker:

A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.

A probable valid biomarker may not have reached the status of a known valid marker because, for example, of any one of the following reasons:

- ***The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny.***
- ***The data …, although highly suggestive, may not be conclusive.***
- ***Independent verification of the results may not have occurred.***

III Exploratory biomarker:

A biomarker that does not match criteria I or II.

FDA, March 2005: Guidance for Industry Pharmacogenomic Data Submissions

DILI as an example

Withdrawals and boxed warnings

1959 Iproniazid

1967 Oxyphenisatin

1970 Ibufenac

1982 Benoxaprofen Ticrynafen

1985 Perhexiline

„Hy's law"

1996 Alpidem

1997 Tolcapone Tolrestat

1998 Bromfenac

2000 Troglitazone Amineptine

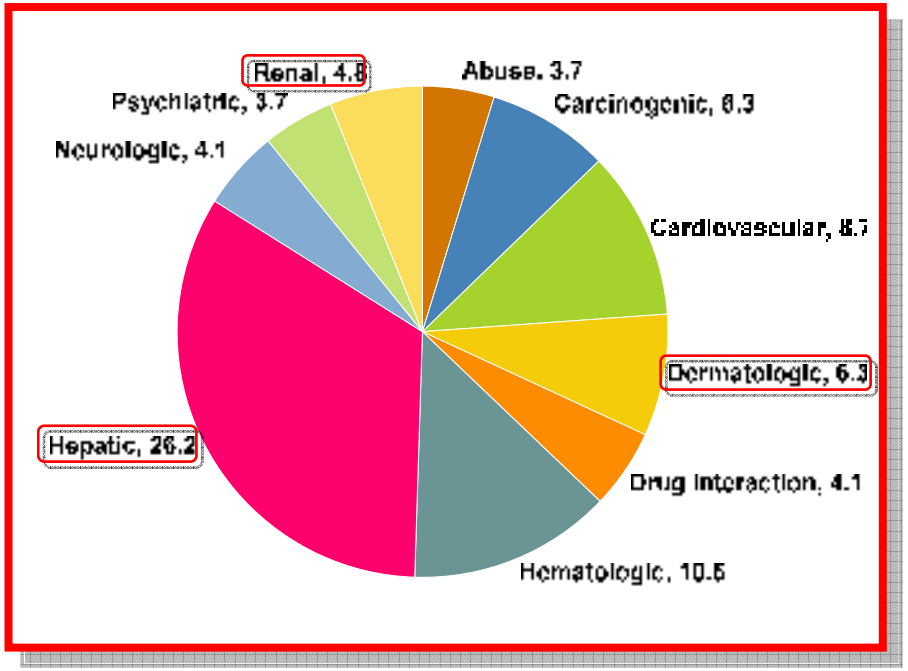
2001 Trovafloxacin

2003 Nefazodone

2005 Pemoline

2006 Ximelagatran

2007 Lumiracoxib

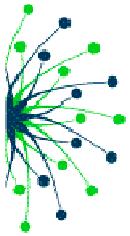


Blackbox warnings

Docetaxel
Nefazodone
Nevirapine
Amiodarone
Adefovir
Divalproex
Methotrexate
Idarubicin
Streptozocin
Isoniazid
Felbamate
Ambrisentan
Epirubicin
Dantrolene

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

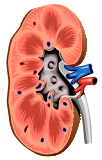
➢ Multitude of patient populations need to be included

Qualification cannot be achieved by one company alone

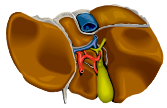
IMI SAFE-T Consortium

Scope

Three organs needing better clinical monitoring of drug-induced injuries:



Kidney: current standards increase only once 50-60% of kidney function is lost.



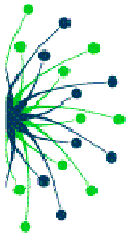
Liver: current standards are not sufficiently sensitive and specific and do not adequately discriminate adaptors from patients at high risk to develop liver failure.

Vascular System: currently no biomarkers available for drug-induced vascular injury in human.

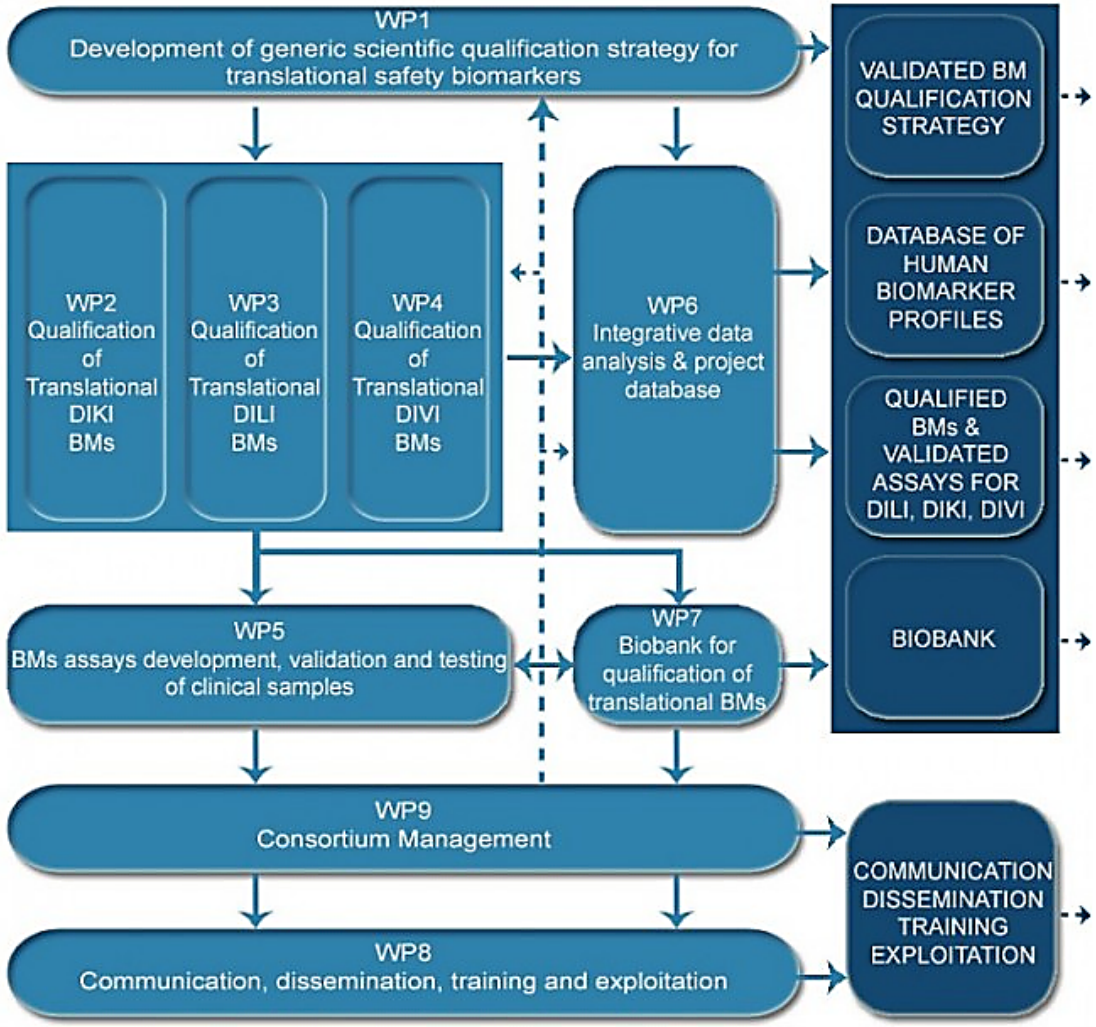
IMI SAFE-T Consortium

Objectives

- To evaluate **utility** of safety BMs for monitoring DIKI, DILI and DIVI **in humans.**
- To **develop assays** and devices for clinical application of safety BMs
- To compile enough evidence to qualify safety BMs for **regulatory decision making in clinical drug development** and in a **translational context**
- To gain evidence for how safety BMs may also be used in the **diagnosis of diseases** and in clinical practice

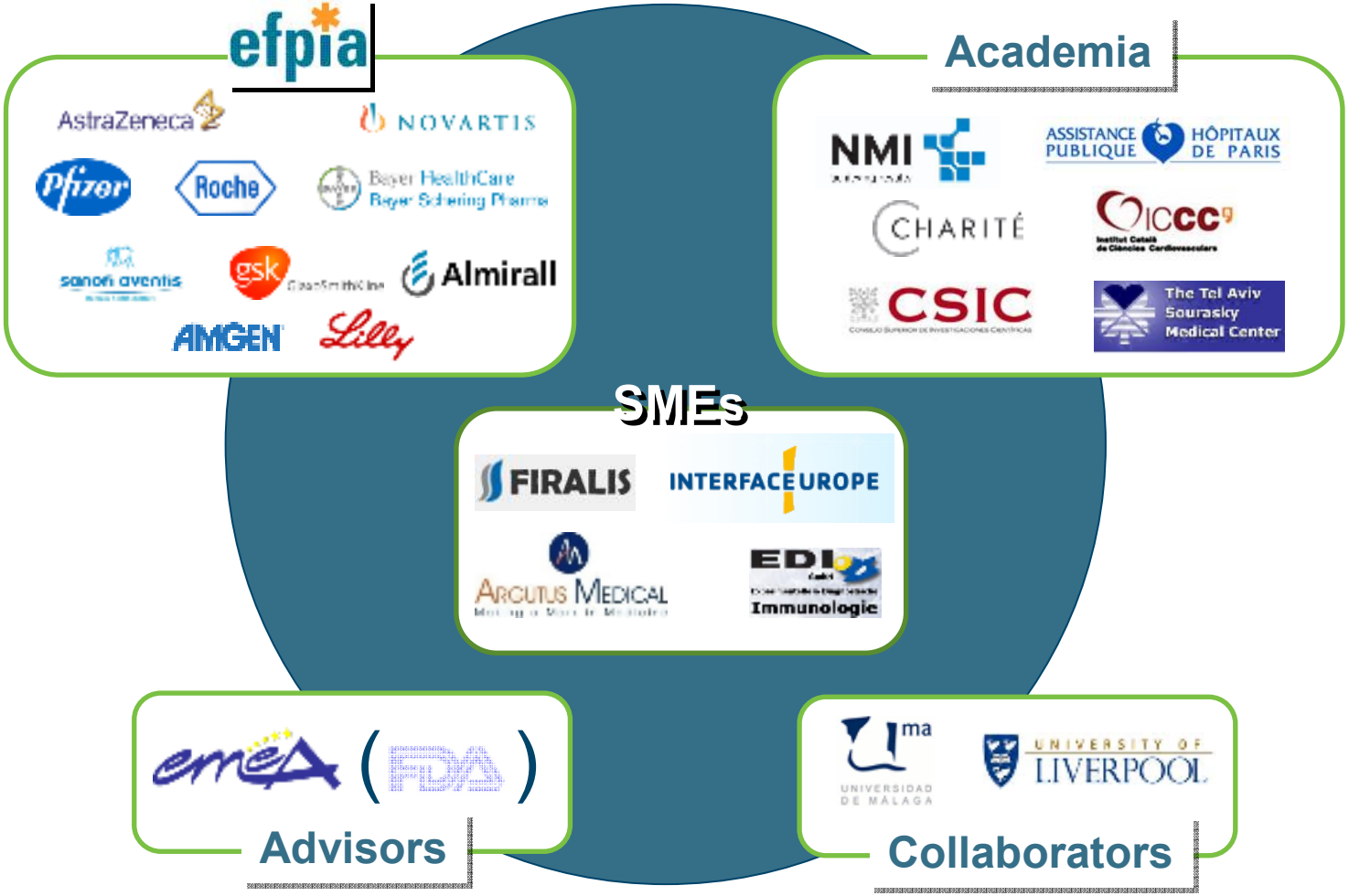


SAFE-T structure and deliverables



- Evidence-based decision making
- More reliable causality assessment
- Better mechanistic understanding
- Safer translation to clinical development
- Earlier and more specific signal detection
- Enhanced clinical monitoring
- ➢ **Improved patient safety**
- ➢ **Reduced attrition rates**
- ➢ **Accelerated and safe approval of innovative medicines**

SAFE-T participants



Funding and timing

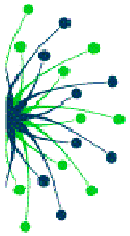
Financing

- 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

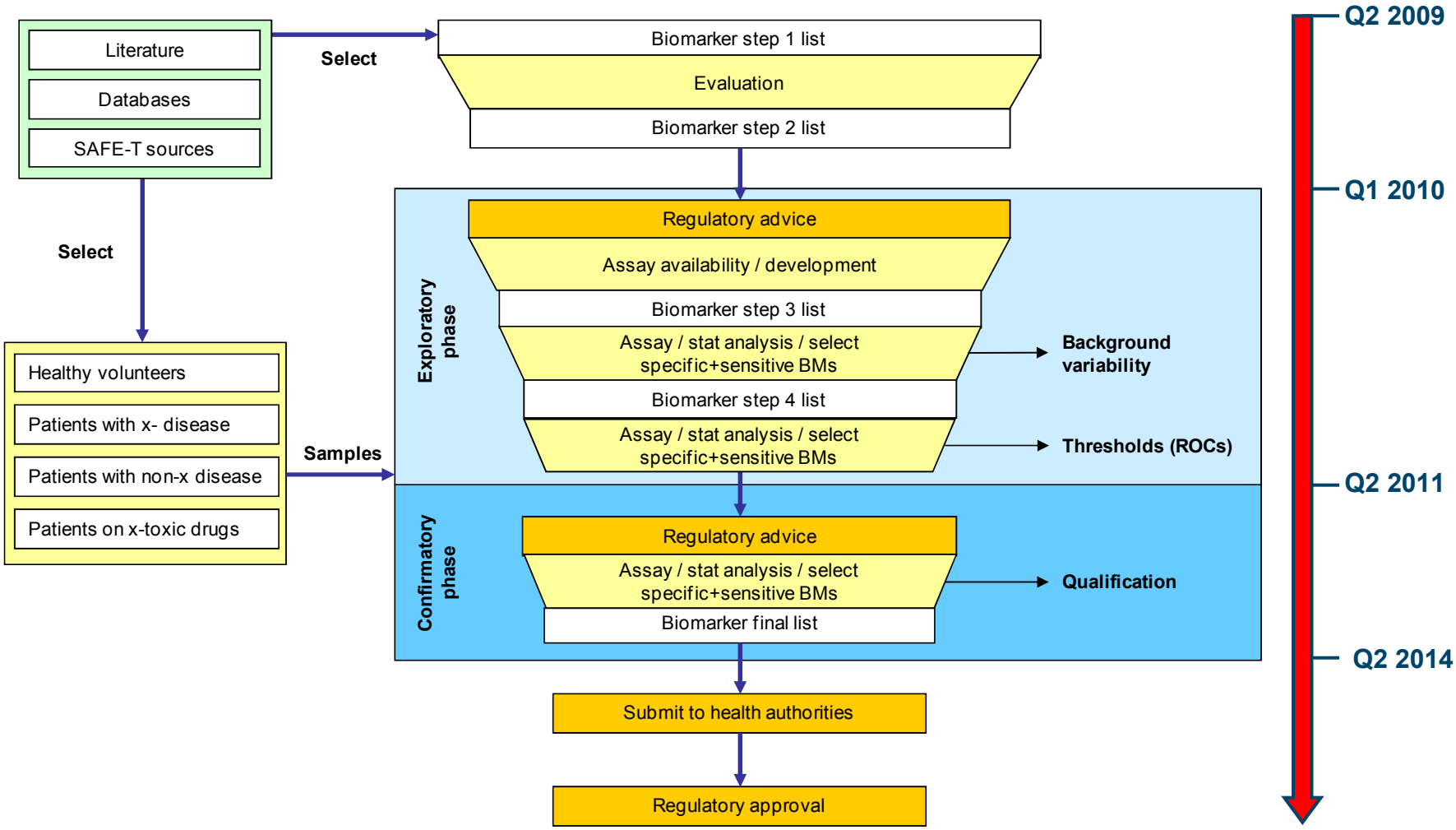
Timing:

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



Biomarker qualification process

Elements and process flow



Biomarker discovery

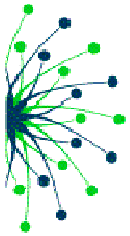
Paralleling qualification

Why?

- Biomarker candidates may not cover all objectives of SAFE-T
  - Lack of susceptibility markers
  - For DILI, lack of sensitive functional markers, some pathologies poorly represented
  - Most markers identified in pre-clinical models

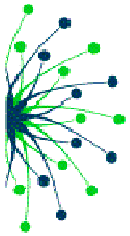
How?

- Based on human cases from SAFE-T clinical studies
- Characteristic changes in serum proteome and metabolome expected
  - Mass spec and protein antibody array analyses of plasma samples planned
- Genetic analysis not planned as yet



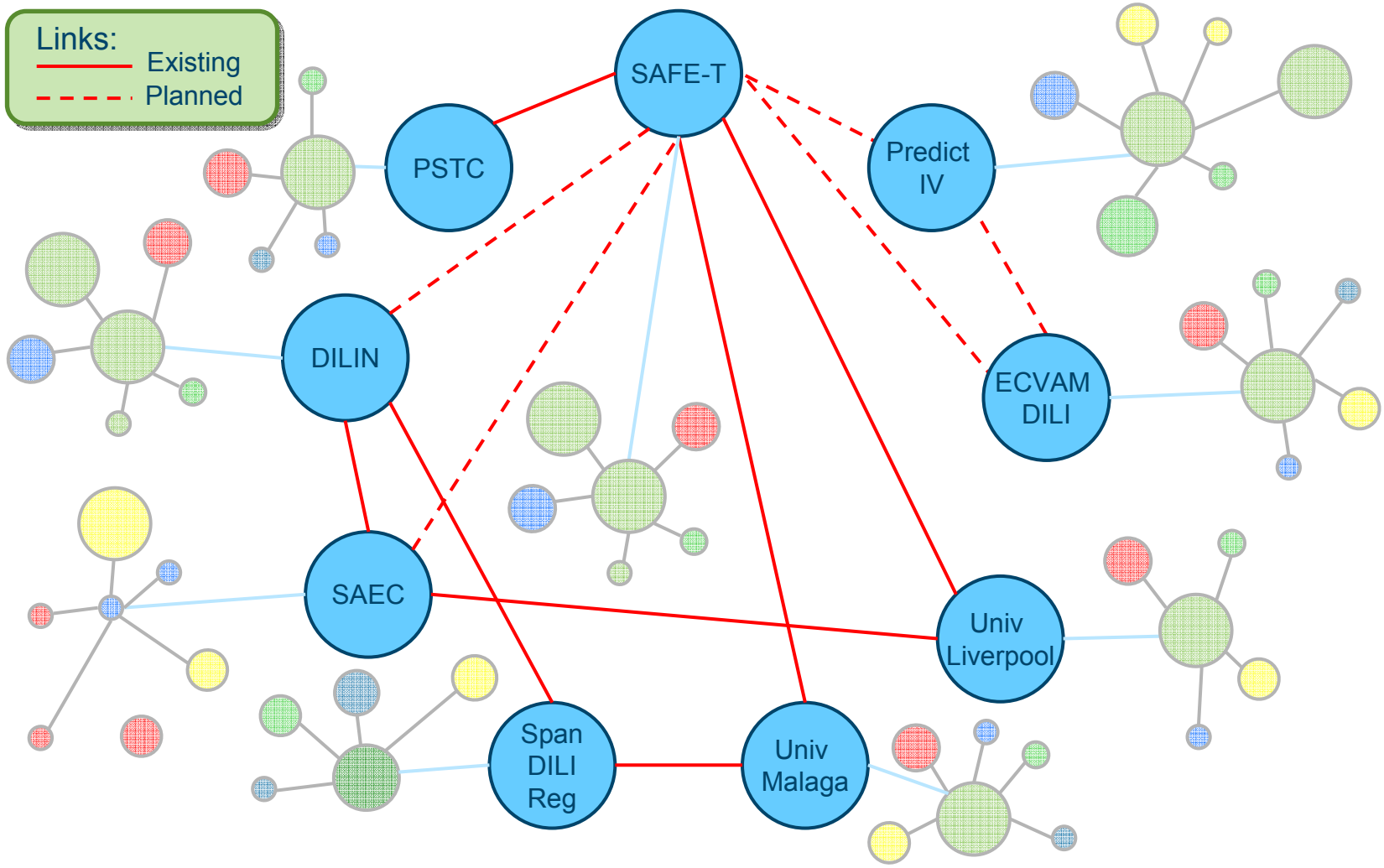
SAFE-T gaps and challenges

- Primary scope is ***clinical*** qualification of ***soluble*** translational safety biomarkers
- Out of scope are:
  - Genetic susceptibility markers
  - Preclinical assay validation
  - Preclinical biomarker discovery
- Case and sample access
  - Particularly for DILI and DIVI, getting access to a sufficient number of suitable cases even within this large consortium may be challenging
  - Logistics to collect samples as close as possible to and around an event will be demanding
  - Other groups and consortia may compete for similar patient populations
- Duplications and overlaps with other consortia need to be avoided



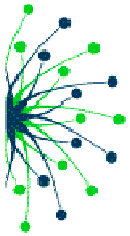
Joining efforts: key to success

SAFE-T's links to other groups and consortia



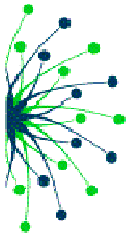
SAFE-T achievements

- Generic qualification strategy defined
- Draft study protocols for prospective studies being prepared
- Initiated regulatory interactions via briefing meetings with EMA/FDA for DILI and DIKI work packages
  - Qualification strategy supported
  - Obtained constructive feedback on how to further improve the qualification process
  - Agencies are interested to see results of exploratory phase studies
- Reached out to other consortia and institutions in order to establish collaborations
  - Goal: utilize synergies, avoid overlaps and duplications
  - Established collaboration with Predictive Safety Testing Consortium (PSTC)
  - In discussion with Serious Adverse Event Consortium (SAEC)



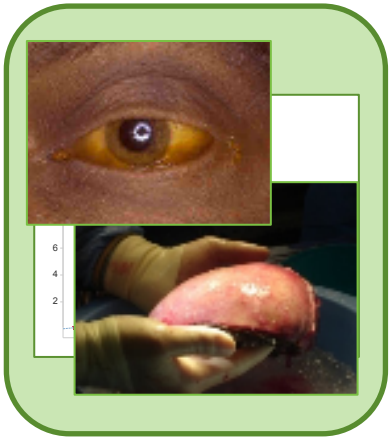
Next steps

- Incorporate regulatory feedback into qualification strategy
- Set up consortium database
- Finalize exploratory phase study protocols
- Initiate prospective studies
- Include sampling into standard clinical trials
- Finalize agreements with other consortia



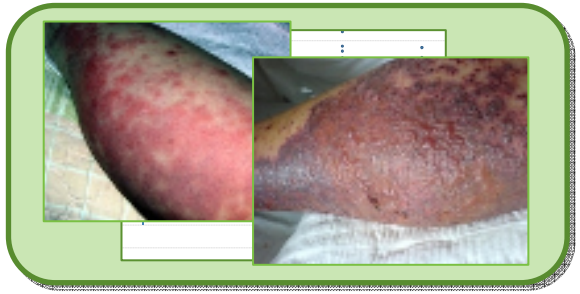
Need for better safety biomarkers

The future perspective



Drug induced liver injury (DILI)
DILI biomarkers

Drug induced kidney injury (DIKI)
DIKI biomarkers



Drug induced vascular injury (DIVI)
DIVI biomarkers

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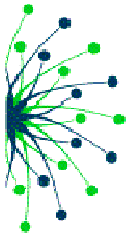
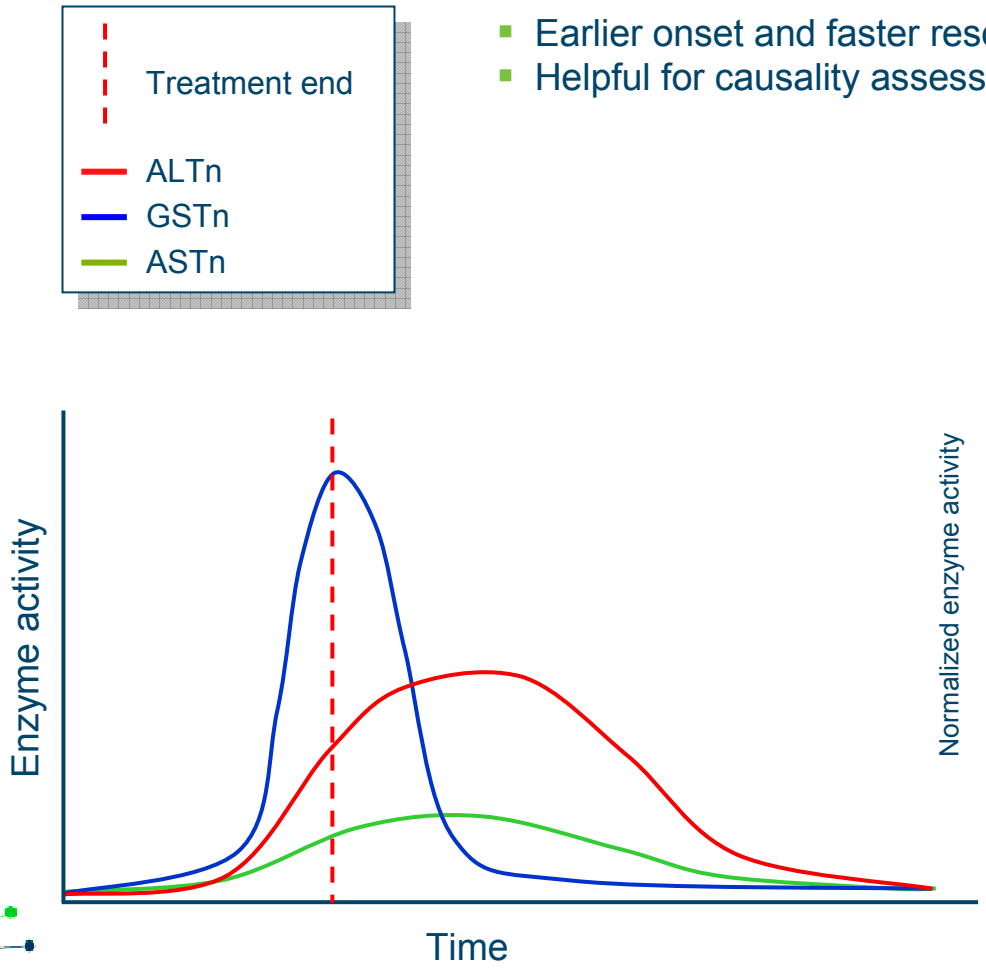
Backups

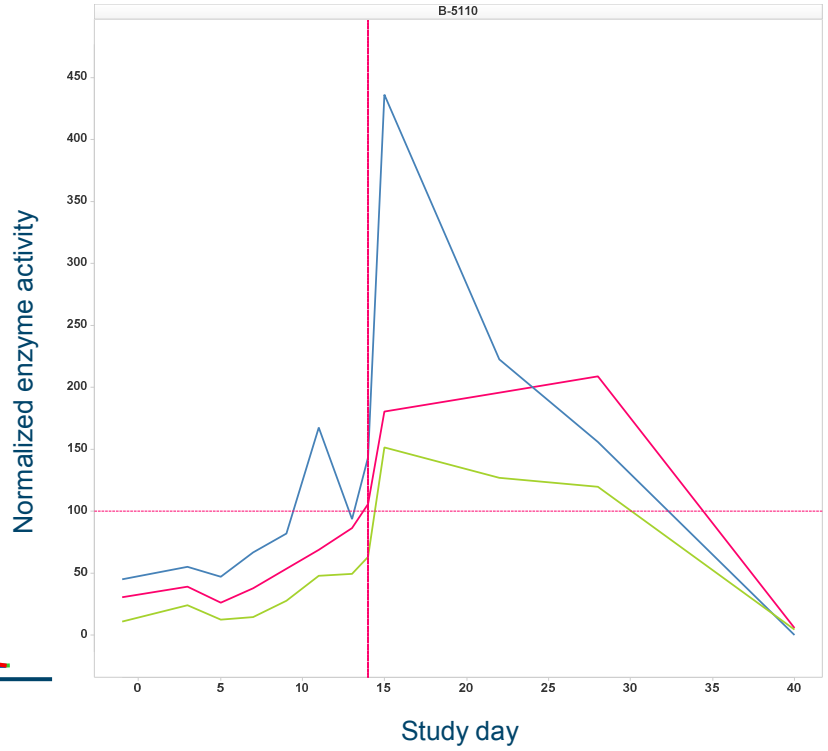


Example Glutathione S transferase α (αGST)

Time profiles as compared to standard markers

- Earlier onset and faster resolution?
- Helpful for causality assessment in a subset of cases?





Biomarker selection process

Example DILI markers