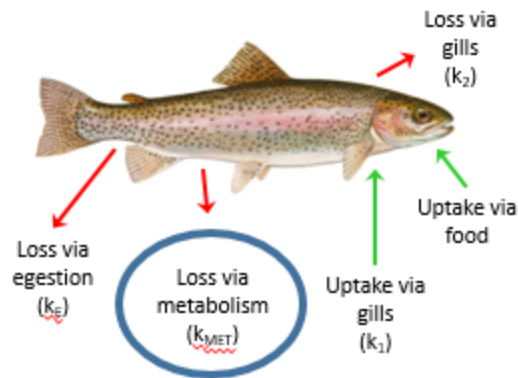


Immunotoxicology Committee Cytokine release assay ring trial

Ellen Evans, PhD, Pfizer



THE TRIAL OF DRUG TESTING: WHAT WENT WRONG?

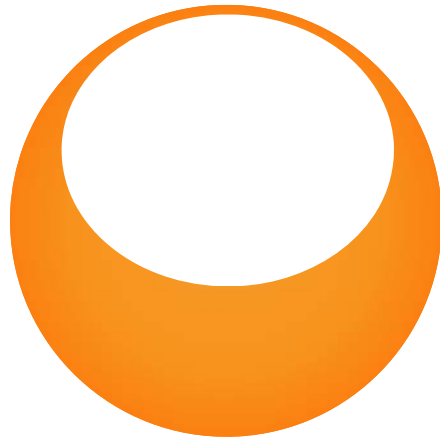
An infographic titled "THE TRIAL OF DRUG TESTING: WHAT WENT WRONG?" illustrating the stages of drug testing and the challenges involved. It features a human figure with yellow arrows indicating the path of a drug through the body.

- 1** **Preclinical testing**: Involves testing a drug on cells and animals. The goal is to identify potential toxicity and efficacy. However, many drugs that pass these tests fail in human trials.
- 2** **Phase I clinical trials**: The first time a drug is tested in humans. The goal is to determine the safe dose and side effects. Many drugs are discontinued here due to safety concerns.
- 3** **Phase II and III clinical trials**: Larger groups of patients are tested to evaluate the drug's effectiveness and compare it to existing treatments. Many drugs are discontinued here due to lack of efficacy or safety issues.
- 4** **Post-marketing surveillance**: After a drug is approved, it is monitored for any adverse effects that were not detected in clinical trials. Some drugs are withdrawn from the market due to these findings.

The infographic includes various diagrams, including a human figure, a cell diagram, and a flowchart, to illustrate the process and the reasons for drug failure.

Bioaccumulation Committee Fish hepatic metabolism ring trial

Kelly Faye, PhD, EPA



ITC: Cytokine Release Assay Ring Trial

Ellen W. Evans, DVM PhD DACVP, Pfizer



Case Study Overview

- How did we get here?
- Why is this important to address now?
- What is the project to address the issues?



How did we get here?

TGN 1412 (CD28
superagonist)
cytokine storm in
phase 1

EMA workshop

HESI ITC Survey
and Workshop

2006

2009

2013

2016



What did the ITC learn?

- No “gold standard”
- Multiple platforms in multiple locations
- Decisions based on MOAs and other needs
- Within an approach: Different conditions
(e.g. standards, dilutions, etc.)



How did we get here?

TGN 1412 (CD28
superagonist)
cytokine storm in
phase 1

EMA workshop

HESI ITC Survey
and Workshop

**Launch of HESI
ITC – NIBSC
standards study**

2006

2009

2013

2016



The National Institute for Biological Standards and Control



- Global leader in the characterisation, standardisation and control of biological medicines.
- UK's Official Medicines Control Laboratory for biological medicines
- World leader in development and production of international standards for biologics
- NIBSC plays a major role in assuring the quality of biological medicines worldwide through the provision of biological reference materials, by testing products and carrying out research.



Why now?

- Qualification & validation of platforms
- Future context
 - Comparison of results between platforms
 - New biotherapeutics
 - Harmonization of existing assays to reduce improper immunotox evaluation



HESI ITC – NIBSC Standards Study

- Institutions already have optimized in-house protocols
- **NOT** looking to change current methodologies

BUT RATHER HAVE A SET OF STANDARDS THAT...



Fit into current assays already in use



Have a response range (low, moderate, high)

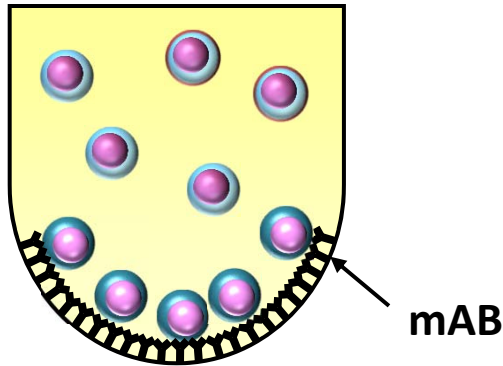
- Standard repository at NIBSC for future availability



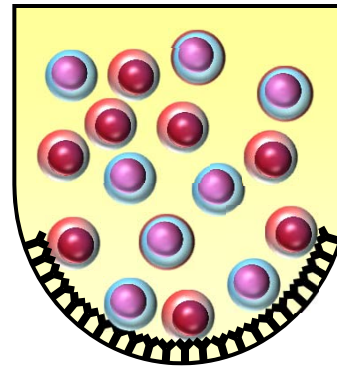
Example of assay formats

mAb in Solid Phase (SP)

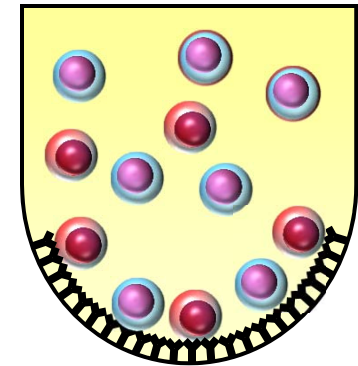
Purified PBMC



Whole blood

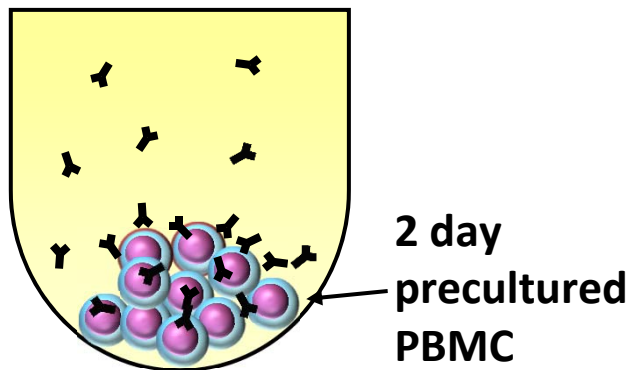


10% diluted blood

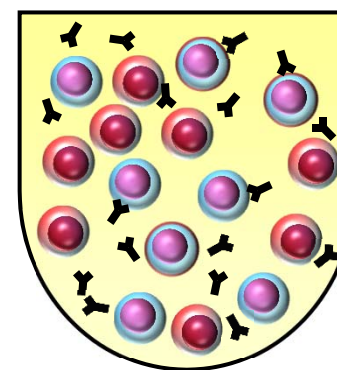


mAb in Aqueous Phase (AQ)

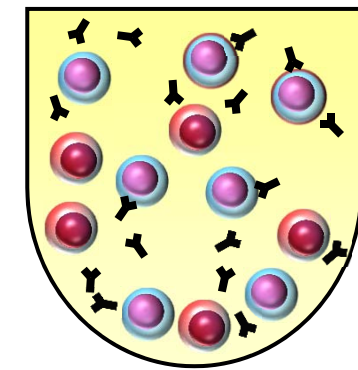
Purified PBMC



Whole blood



10% diluted blood



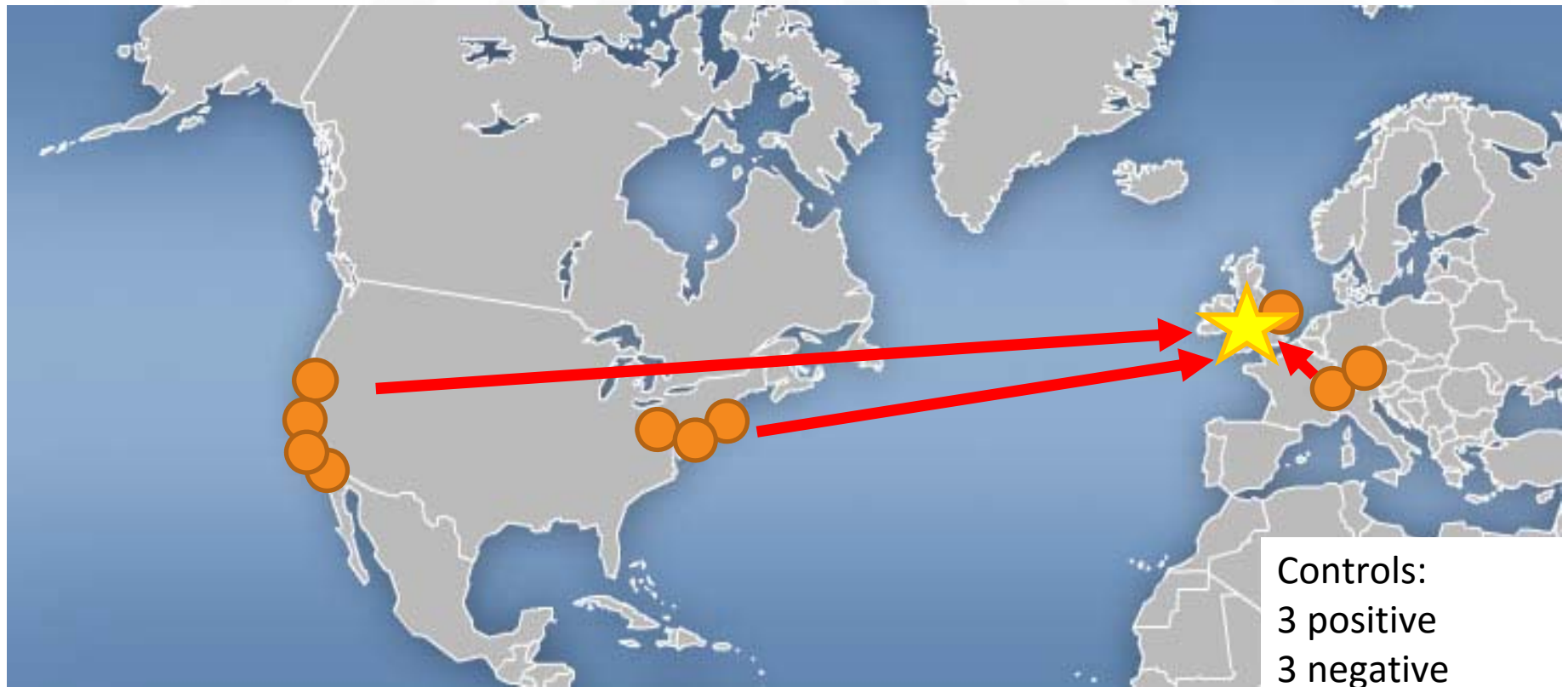
Stebbing et al J. Immunol 2007; 179:3325-3331

How well do these standards perform across platforms, and in comparison to in-house controls

What standards will be evaluated?

- Positive Controls
 - Anti-human CD52 mAb; Human IgG1 (Mild cytokine release)
 - Anti-human CD3 mAb; mouse IgG2a (Moderate cytokine release)
 - Anti-human CD28 mAb: human IgG4 (severe cytokine release)
- Negative Controls, non-specific human anti-4-hydroxy-3-nitrophenyl acetyl (NP) isotypes
 - Human anti-NP; IgG1,
 - Mouse anti-NP; IgG2a,
 - Human anti-NP; IgG4
- 10x PBS (Gibco, ref 70013-016, lot 1697466)

HESI ITC – NIBSC Standards Study



GOAL: Data gathered June – September 2016 with publication in 2017



Summary

Hazard – cytokine storm

Efficient – quick study and incorporation into existing methods

Standards – incorporating a set of standards to allow for harmonization and future evaluation

Integrity – repository for future use and data confidence across platforms

