EU NCL
Nanomedicine Characterisation Laboratory

Perspectives on the Start-Up of EU-NCL

Susanne Bremer

FIP/USP/AAPS Workshop on Nanomedicines-Technical and Regulatory Perspectives, March 20-22, 2017

Nanomedicines in the European Translational Process

R&D

130 projects
€ 600m

6500 patents
500 SMEs

Market

30 marketing authorisations

50 scientific advices

120 clinical trials

TRANSLATIONHUB

European Nanomedicine Characterisation Laboratory

GMP manufacturing for clinical trials

Translation advisory board

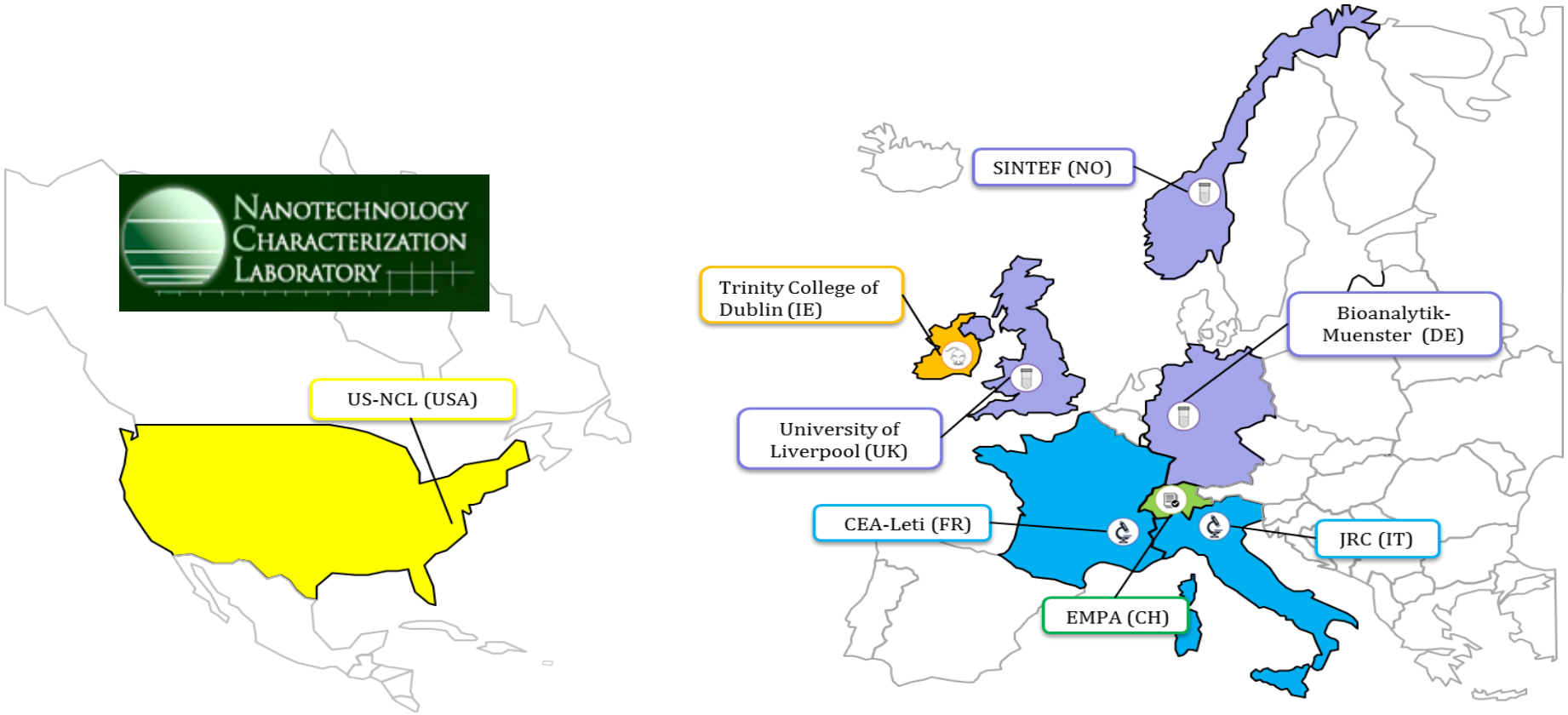
EUNCL

Aims and Objectives

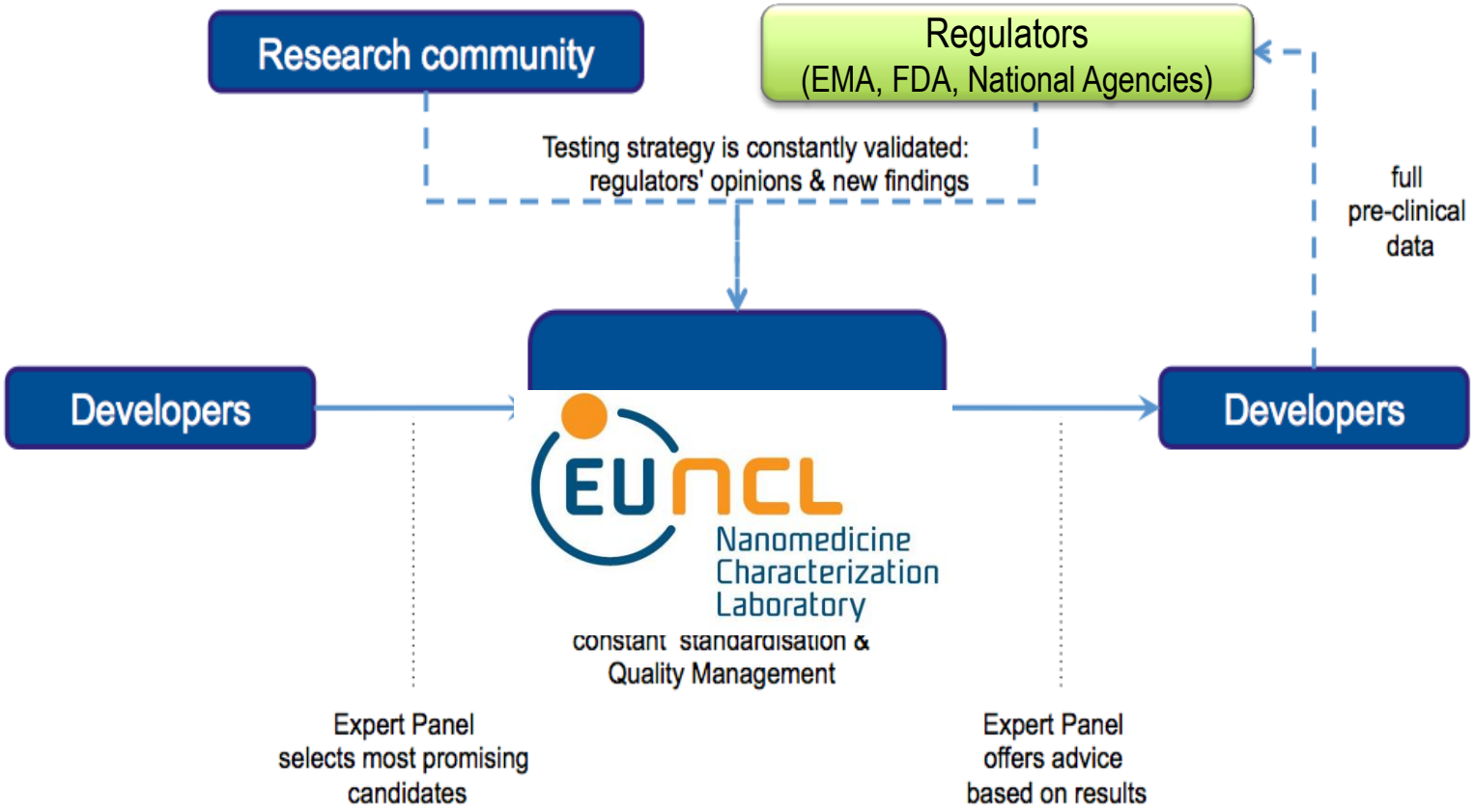
To accelerate translation of engineered nanoparticles for medical applications to the market through

- standardized pre-clinical characterization of nanomaterials intended for medical therapies (free of charge)
- improved data quality of IMP applications by using standardised methods
- supporting product developer by addressing feedback of decision makers regarding nanospecific properties
- Identification and characterisation of critical parameter related to nanomaterial interaction with biological systems

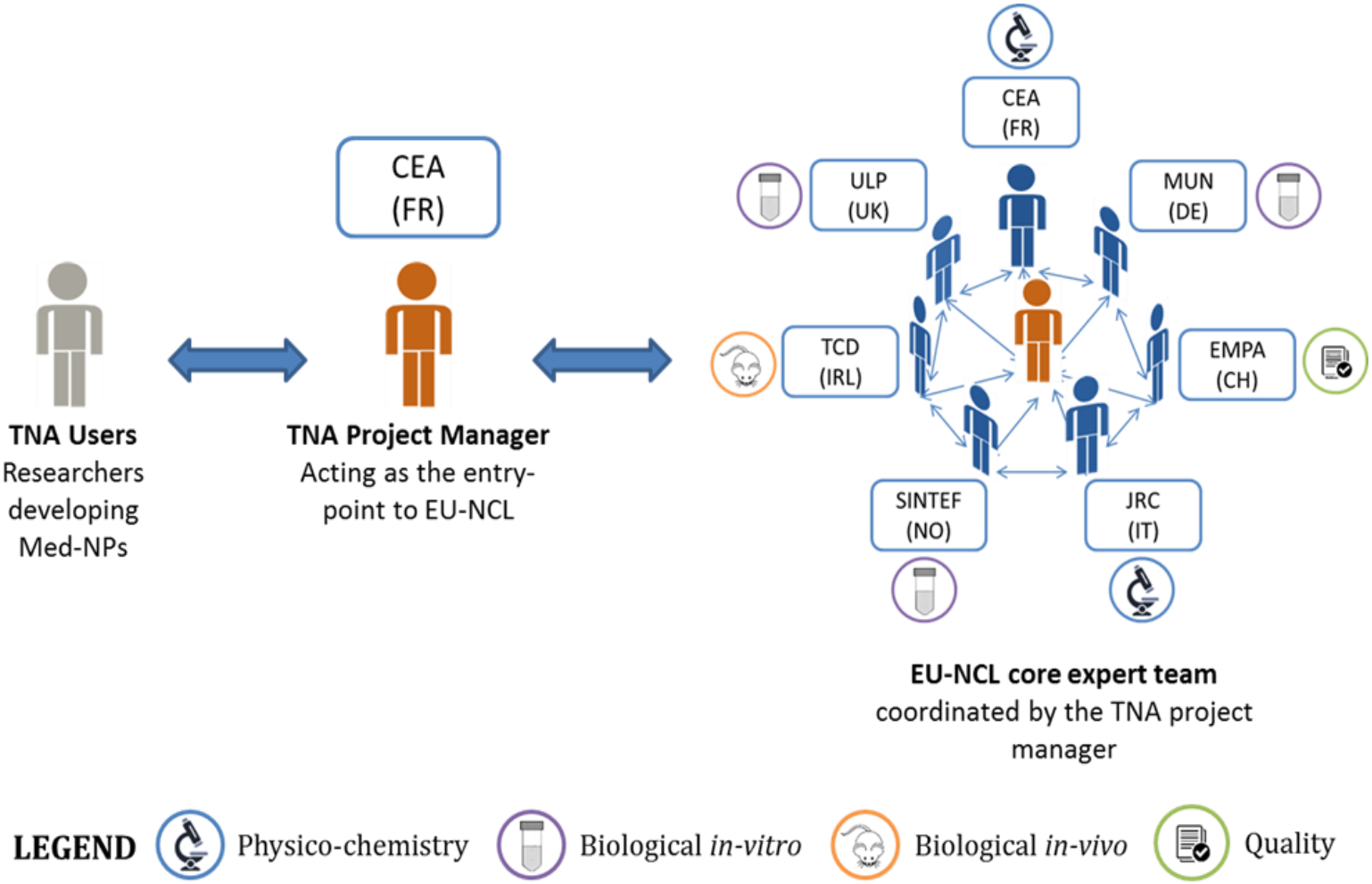
Who we are (core partners)



EU-NCL Concept



How does EU-NCL work



Who can apply?

Academics

Inventors

Startups

SMEs

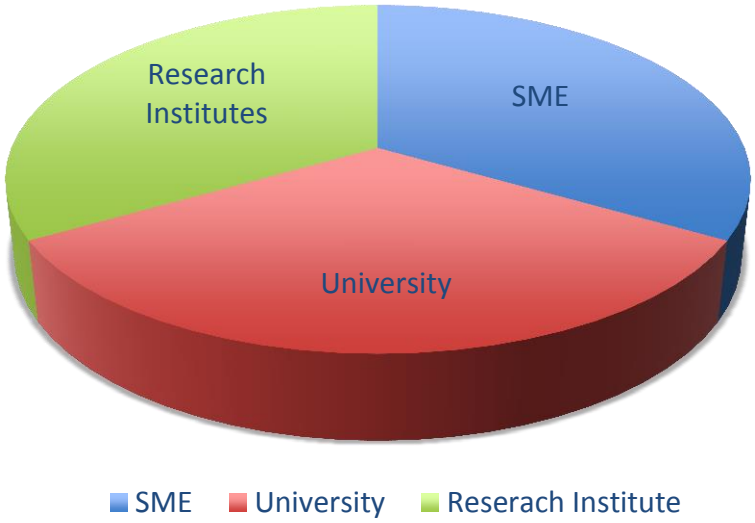
Acceptance criteria:

- Demonstrate the efficacy of the Med-NP in biological systems
- Ability to produce two independent batches (reproducibility)
- Provide a detailed production plan and its scaling up plan
- Propose a clear strategy to transfer the technology to the clinical environment

Next cut off: April 2017

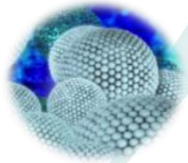
Application profiles

- First TNA campaign launched early 2016
- 9 applications in total
  - 6 eligible
  - 5 progressed to step 2
- Types of materials submitted;
  - Organic (liposomes, dendrimers…)
  - Inorganic (GNP, Iron carbide…)
  - Various drugs loaded

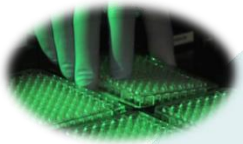


- What makes a successful application?
  - **data and data quality**

What does EU-NCL offer?



Candidate nanomedicine

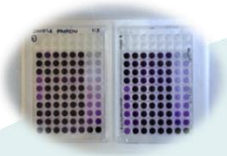


Prescreen

PCC

- Size
- Surface potential
- Purity
- Surface morphology
- Composition

….



In vitro

Haematology/ Immunology/ Cytotoxicity

- Oxidative stress,
- Membrane permeability
- Mitochondrial dysfunction
- Complement Activation
- Coagulation properties
- Hemolytic properties

-…

In vivo

-PK Biodistribution

-Immunogenicity Toxicity

-Pharmakokinetic

…

Final report

Standardized SOPs

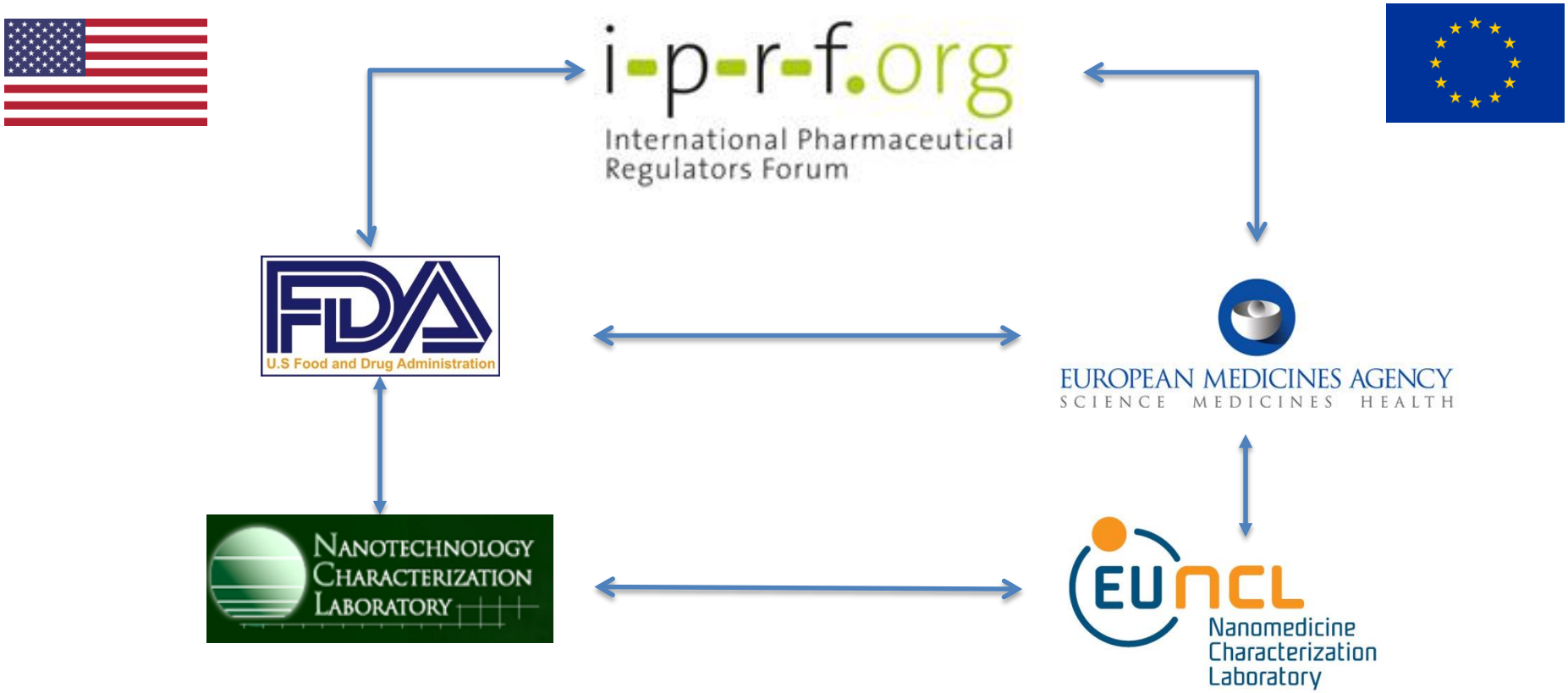
Step1
- Definition/transfer of the SOPs and of the quality controls
- Qualification: inter-laboratory comparison

Step2
- "Bugged" samples to test our problem solving capability

Step 3
- Validation of the laboratories (comparison with results from NCI-NCL)

Nearly 30 Standard Operating Procedures (SOPs) have been qualified in all the laboratories of the EU-NCL consortium and are published on the EU-NCL website

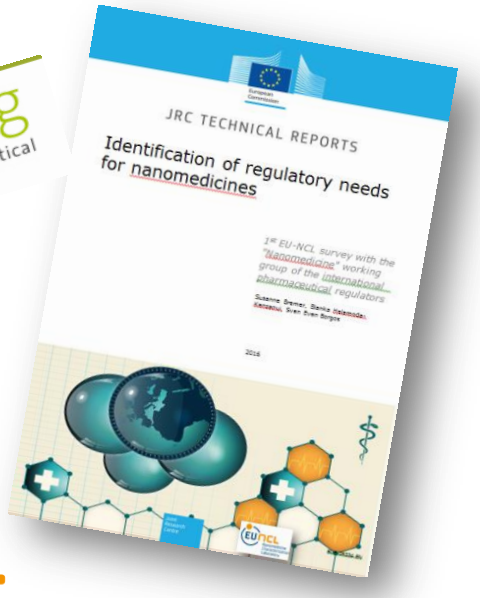
Regulatory network



Survey with the „nanomedicine“ working group of the international pharmaceutical regulatory forum

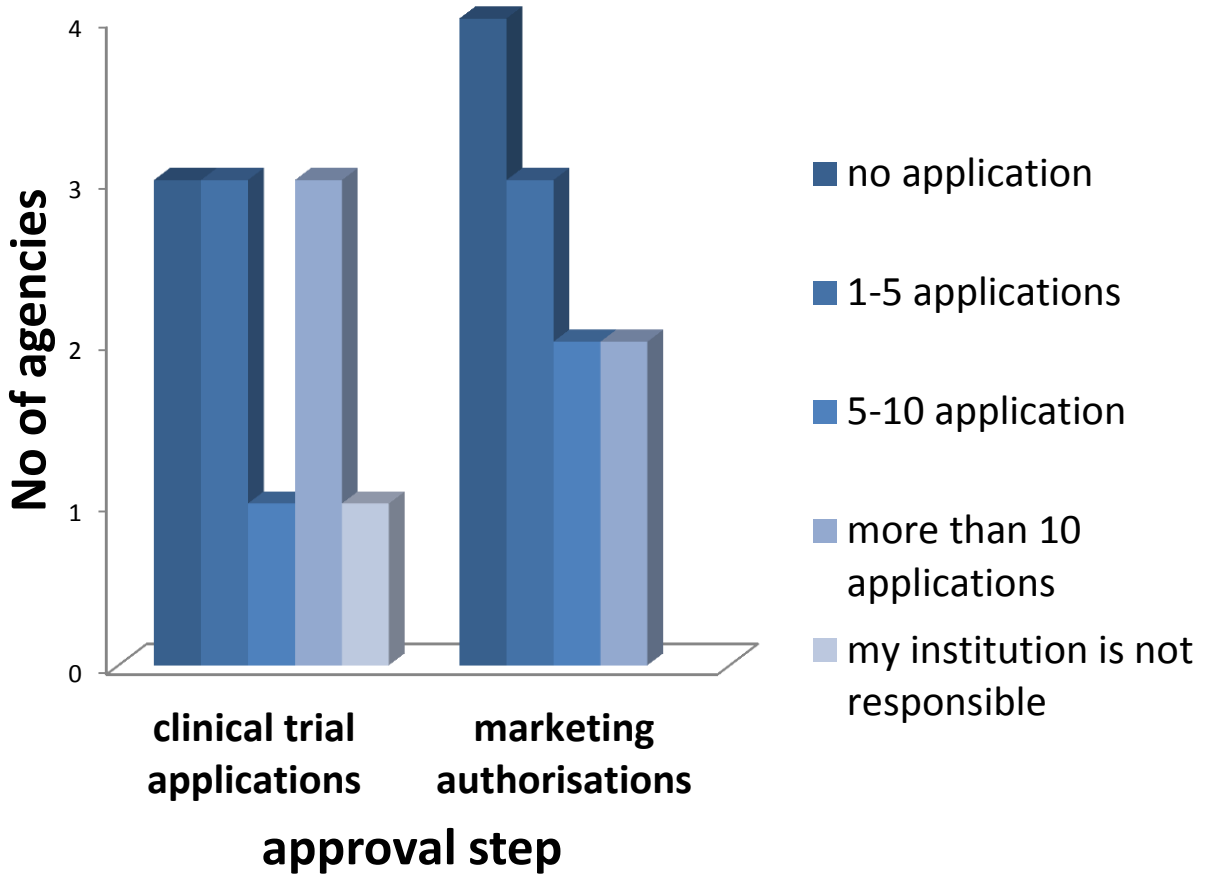
30 Questions to the working group "nanomedicine" of IPRF:

- Addressing current status of applications
- First recommendations of the regulators on information needs
- Expectations of regulators



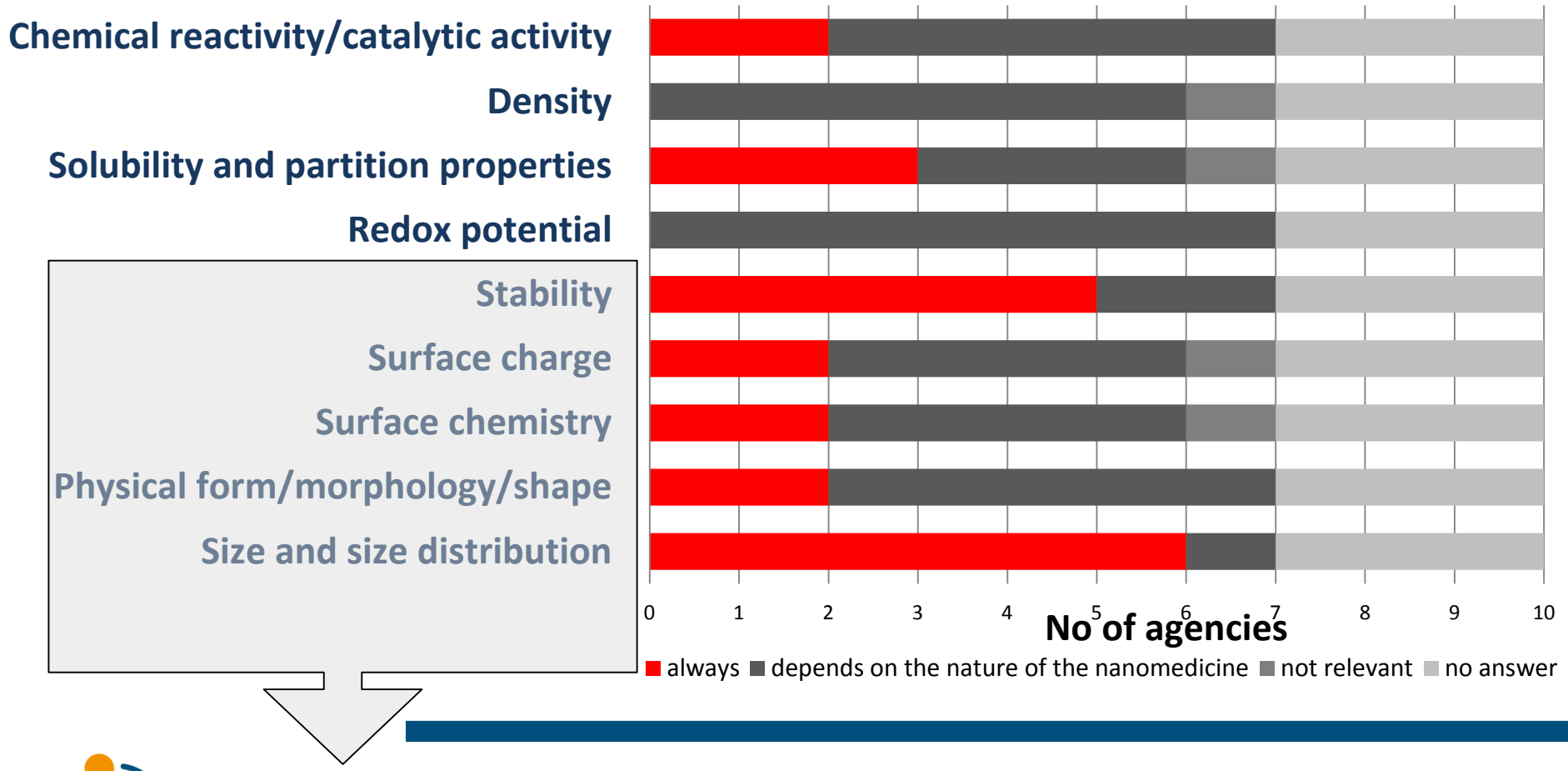
No	Governmental organisation
1	Health Canada (Market Health Products), Canada
2	European Medicines Agency
3	Swiss Agency for Therapeutic Products (Switzerland)
4	Health Canada (Health Products and Food Branch), Canada
5	United States Food and Drug Administration, USA
6	Pharmaceuticals and Medical Devices Agency, Office of New Drug II; Japan
7	Brazilian Health Surveillance Agency, Brazil
8	Ministry of Food and Drug Administration, Korea
9	Center for Drug Evaluation, Taiwan
10	National Institute for Public Health and the Environment, Netherlands
11	Federal Institute for Drugs and Medical devices, Germany
12	The Medicines and Healthcare products Regulatory Agency, United Kingdom
13	National Health laboratory, Luxembourg
14	Spanish Medicines Agency, Spain
15	Ministry of Health, labour and welfare, Japan
16	Australian Government, department of Health therapeutic goods administration, Australia
17	National Agency for food and drug administration and control, Lagos
18	Health Science Authority, Singapore

Applications for regulatory approval

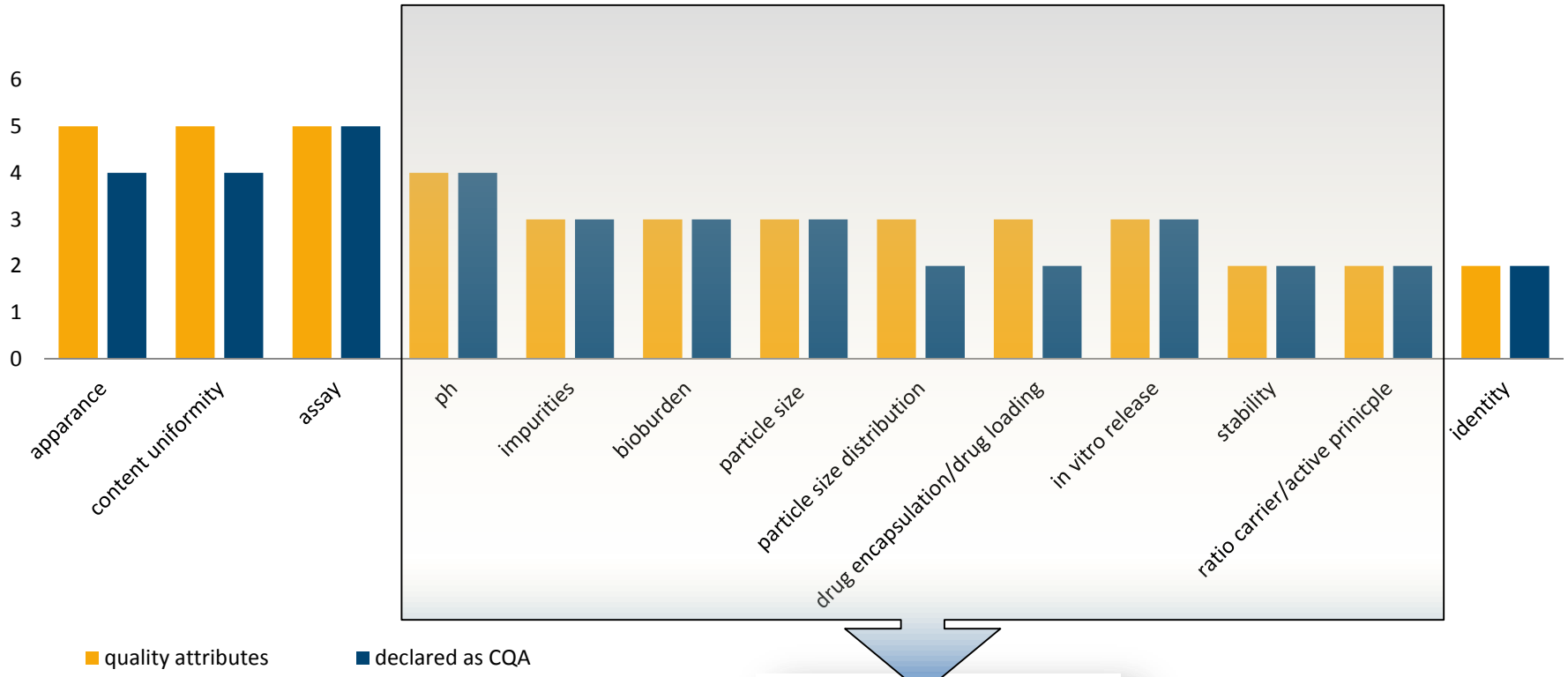


Regional differences in the number of applications!

Which physicochemical properties do you consider relevant for the preclinical characterization of nanomedicines that are not applicable to other pharmaceutical product classes



Critical Quality Attributes

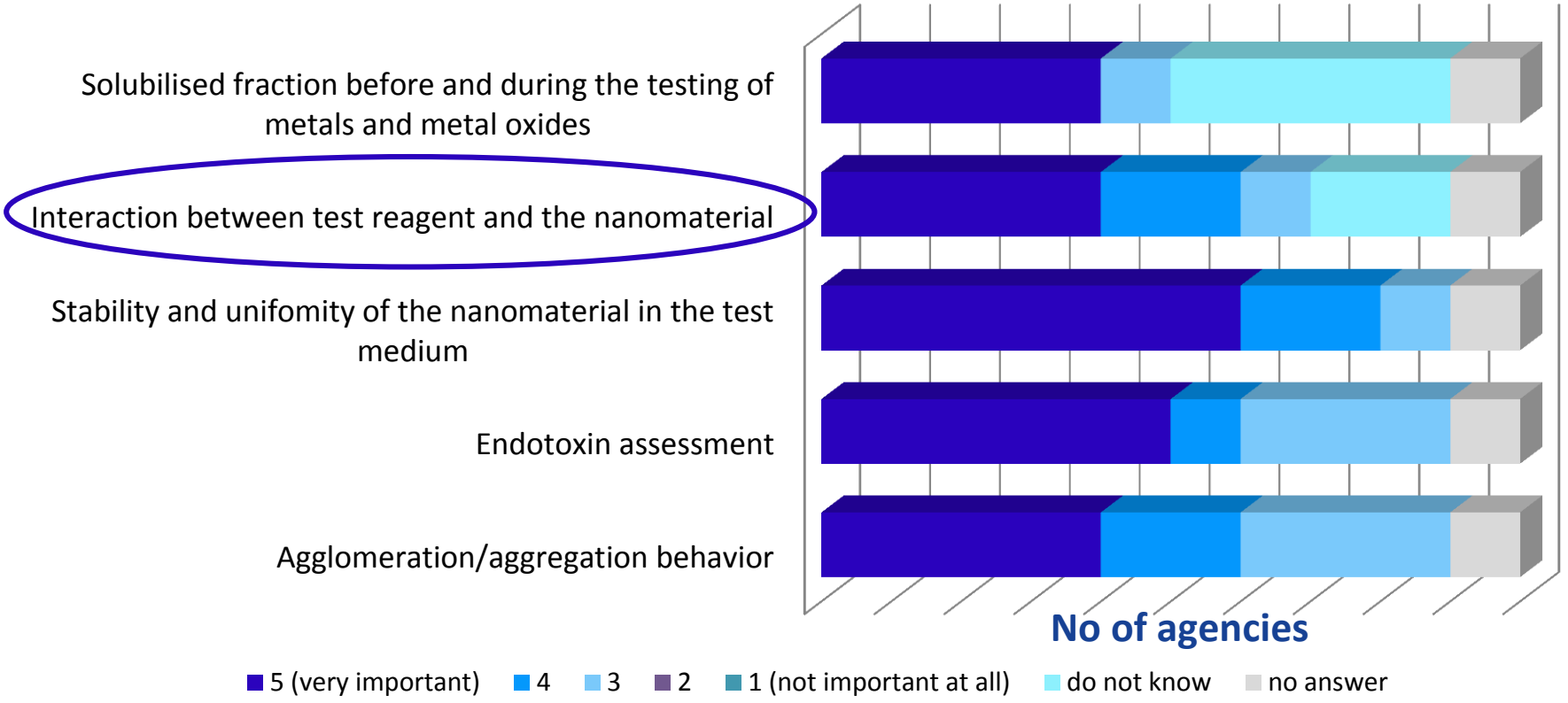


EUNCL Nanomedicine Characterisation Laboratory

- Reviewed 15 European eCommon technical documents
- 7 dossiers have defined CQAs
- In total 50 CQAs have been defined by product developer

i-p-r-f.org International Pharmaceutical Regulators Forum

How do you value potential pitfalls for toxicity testing (in vitro/in vivo) in market authorisations?



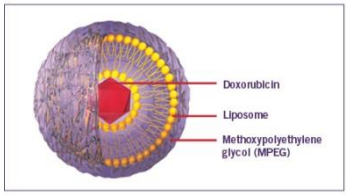
Example: Cytotoxicity

- Inherent toxicity of the formulation in early phases of product development
- Residual excipients resulted from the manufacturing process
- Provide indication on the stability of the product

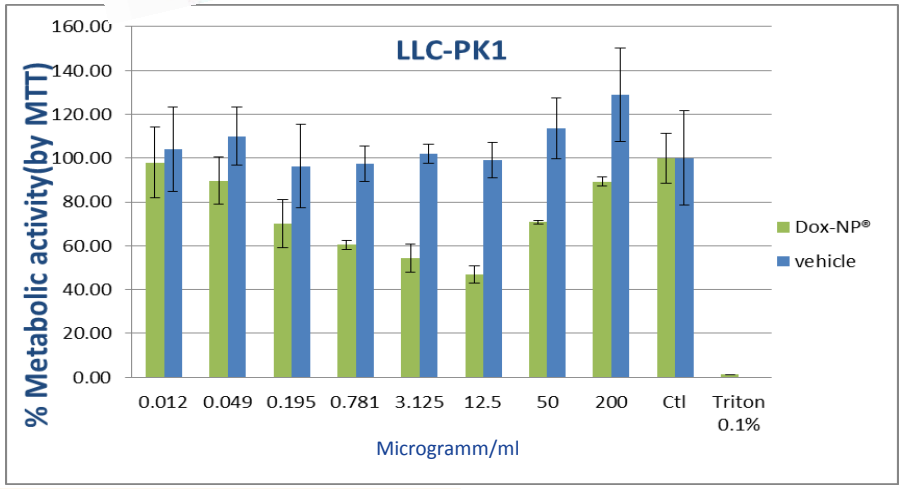
Standards:

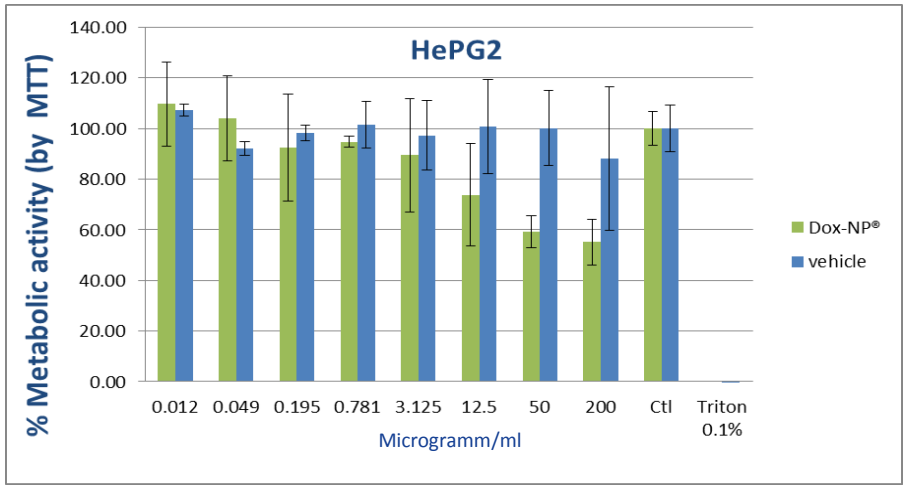
ISO 10993-5:2009
Biological evaluation of medical devices — Part 5: Tests for *in vitro* cytotoxicity

ASTM E2526-08
Standard Test Method for Evaluation of Cytotoxicity of Nanoparticulate Materials in Porcine Kidney Cells and Human Hepatocarcinoma Cells



Case Study: "Doxil"

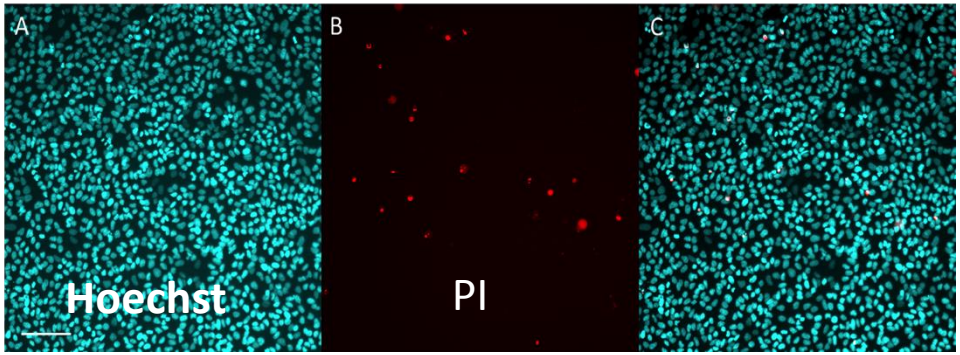




Alternative: High Content Imaging

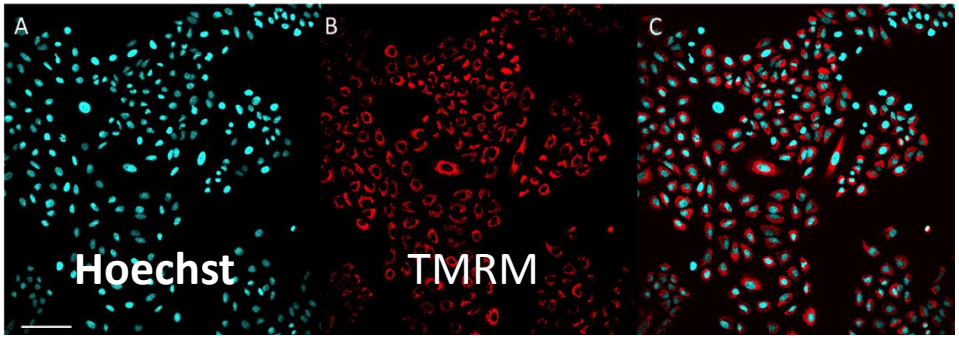
Alternative to the LDH assay:

Viability assay using Hoechst-propidium iodide staining

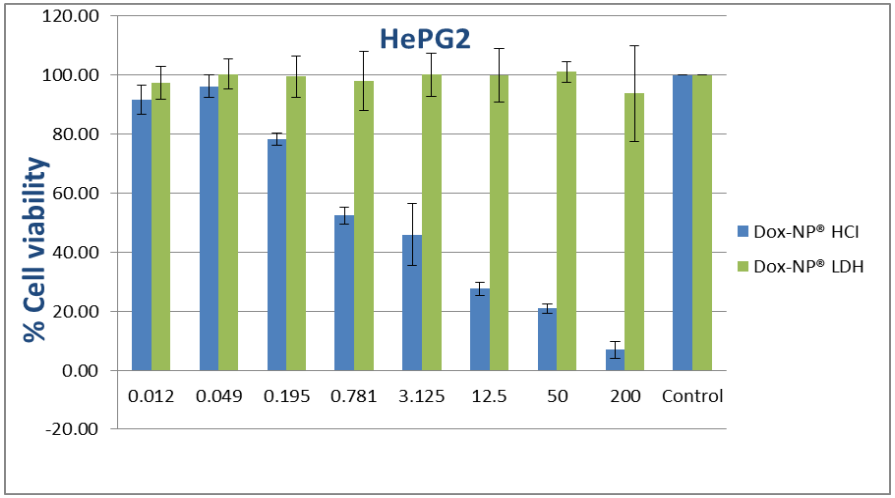


Alternative to the MTT assay:

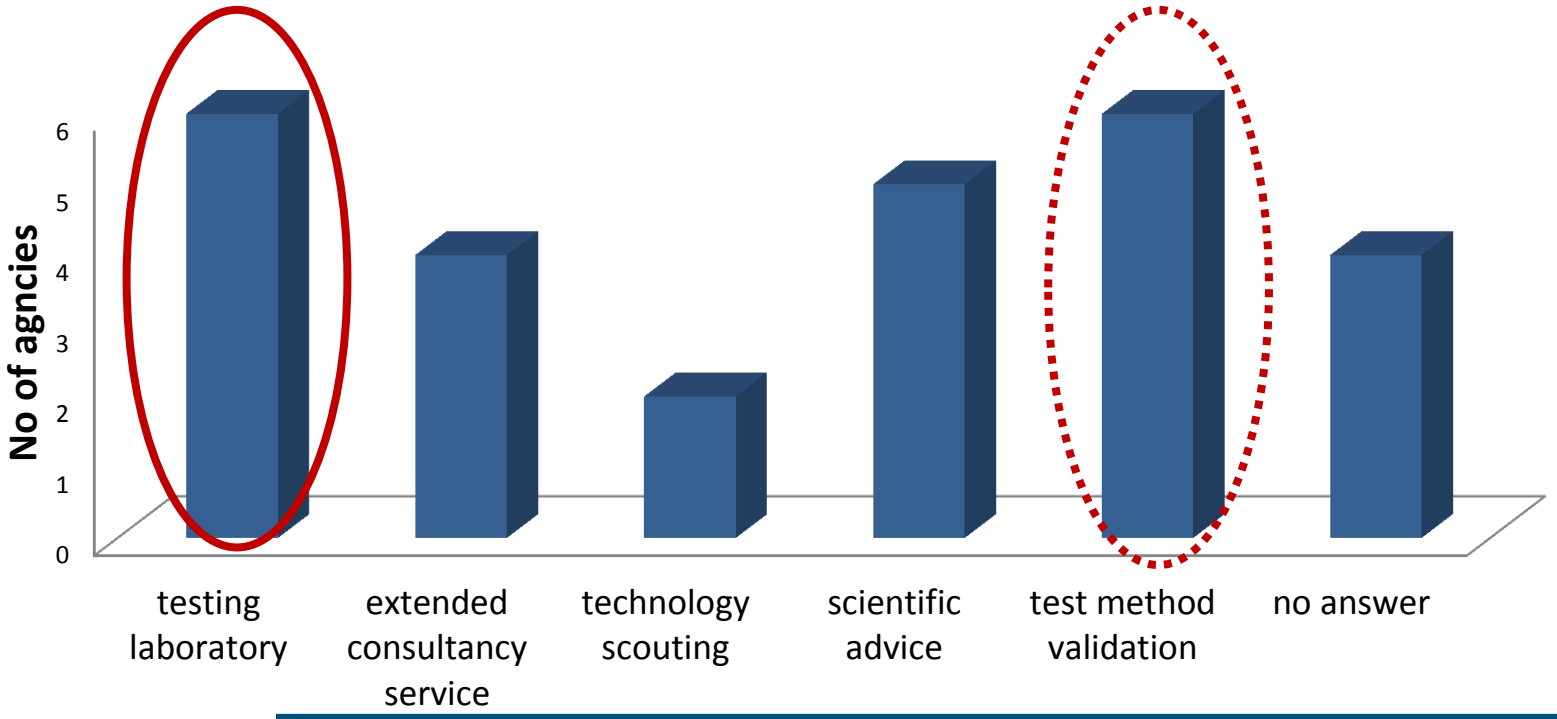
Tetramethylrhodamine, Methyl Ester (TMRM) accumulates in active mitochondria with intact membrane potentials



Comparison of LDH/HCl



What functions could an EU-NCL fullfill to support regulatory authorities…..



Advancing regulatory science

- Assessing and improving the performance of existing standards for nanomedicines e.g. cytotoxicity
- Hands-on experience on the performance of new methodologies
- Harmonising EU-NCLmethods with the NCI-NCL will support their regulatory acceptance
- Gaining knowledge on critical information needs of next generation nanomedicines related to quality and safety and raising regulatory awareness

Benefits of US-EU Cooperation*

Leverage US-NCL historical knowledge

- ~10 years of characterization experience.
- Nearly 300 nanomaterials tested, 6 now in clinical trials.

Quality Control

- Not duplicating efforts, leverage scale up resources, reduce risk of adverse events.

Visibility & Access

- United effort will have expanded visibility to users, Pharma, VC, R&D community, and regulatory agencies (EMA & FDA).
- Pharma is global; based mostly in EU and USA.
- Both US- and EU-NCL will benefit from new/expanded relationships with government-industry consortia & global Pharma.
    - Investments in nanotech from VC & Pharma.

* ***Scott E. McNeil, Director, Nanotechnology Characterization Lab (NCL), April 9, 2013***

Summary

- 6 European laboratories have opened their state-of-the-art infrastructure
- EU-NCL offer a service free of charge to the nanomedicine community
- A core expert team with complementary expertise provides knowledge to product developer
- Nearly 30 assays adressing physicochemical and biological questions have been standardised and are constantly updated according to scientific progress
- Raise regulatory awareness on upcoming challenges with the quality and safety evaluation of nanomedicines
- Establishment of the EU-NCL benefits from the 10 years experience of the NCI-NCL
- The collaboration of NCI NCL and EU NCL will contribute to the harmonisation of information requirements and test methods

Contact

tna@euncl.eu
www.euncl.eu

Contact in USA

mcneils@mail.nih.gov

EUNCL is funded under H2020 Framework programme under grant agreement No 654190

Thank you

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 654190.