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12th Anual ECOPA Workshop
"The Future of 3Rs – From Innovation to Validation"
Session III: The Process of Validation
The Point of View of the Pharmaceutical Industry

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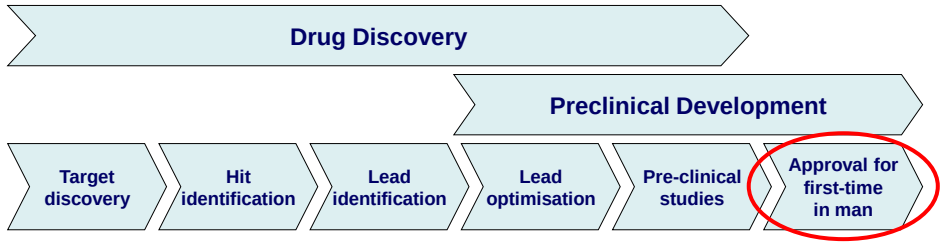
First words

This presentation reflects a PERSONAL OPINION

This presentation does not reflect at all a GENERAL POSITION of the pharma industry

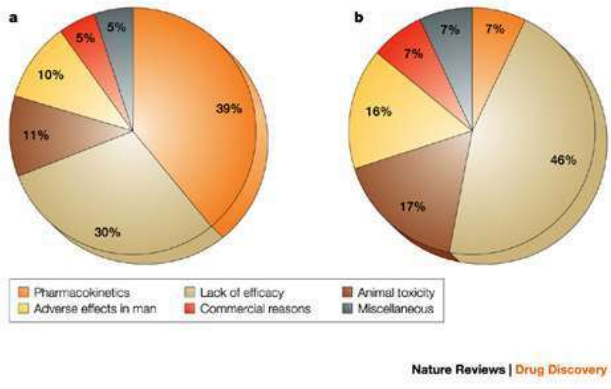
INTRODUCTION (1)

Product development: A complex process



Clinical development:

HOWEVER, WE FAIL IN OUR OBJECTIVES!



Lack of efficacy: 46%

Safety: 33%

(1964-1985)

- **a** | 198 NCEs in clinical development by large UK companies, 1964–1985. **b** | 121 NCEs, excluding the anti-infectives from diagram **a**. (Source: Centre for Medicines Research; redrawn from Ref. ***Nature Reviews Drug Discovery*** **2**, **665-668 (August 2003)**).

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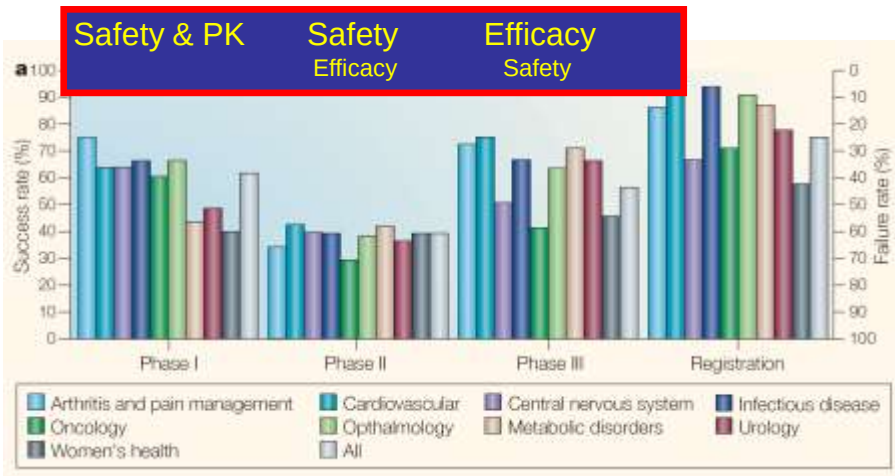
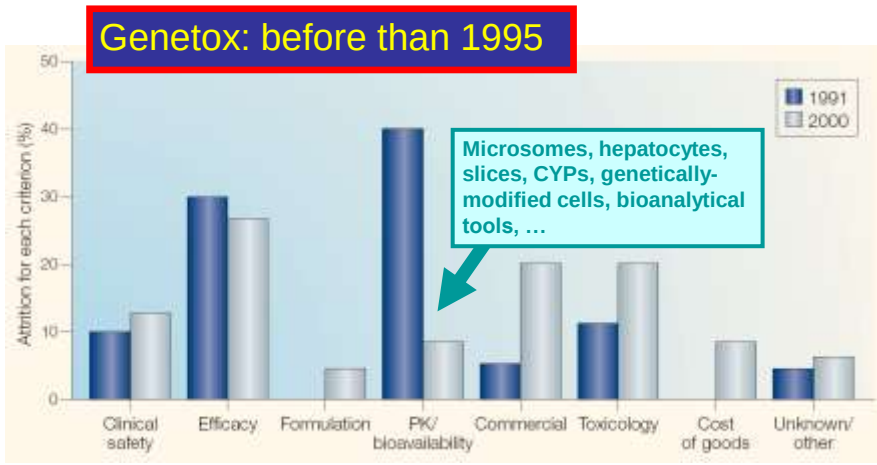


Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat.Rev.Drug.Disc. Aug 2004.

THERE IS A POSITIVE IMPROVEMENT…



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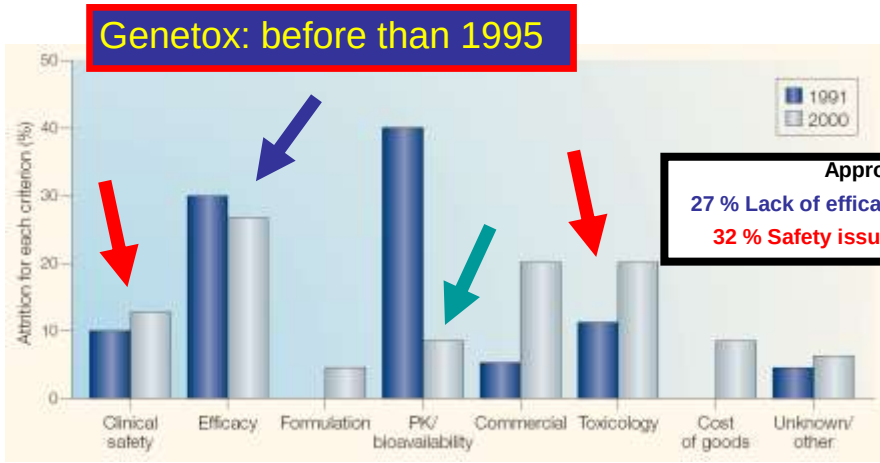

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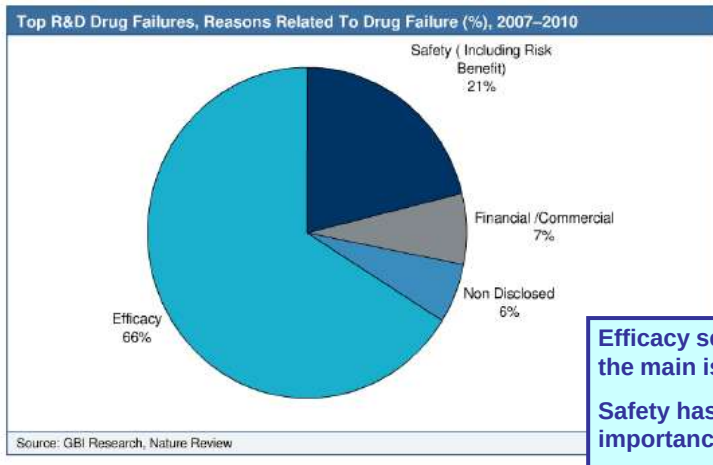
LACK OF EFFICACY AND RISK ACCOUNT FOR MAJOR FAILURES IN DEVELOMENT

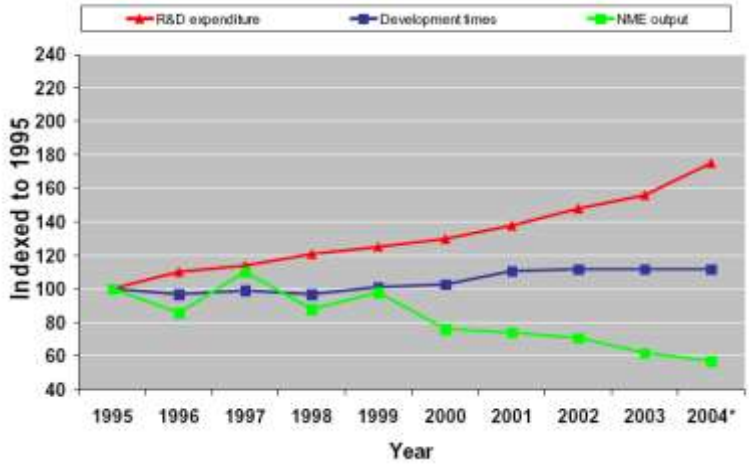


Efficacy seems to be the main issue.

Safety has reduced importance.

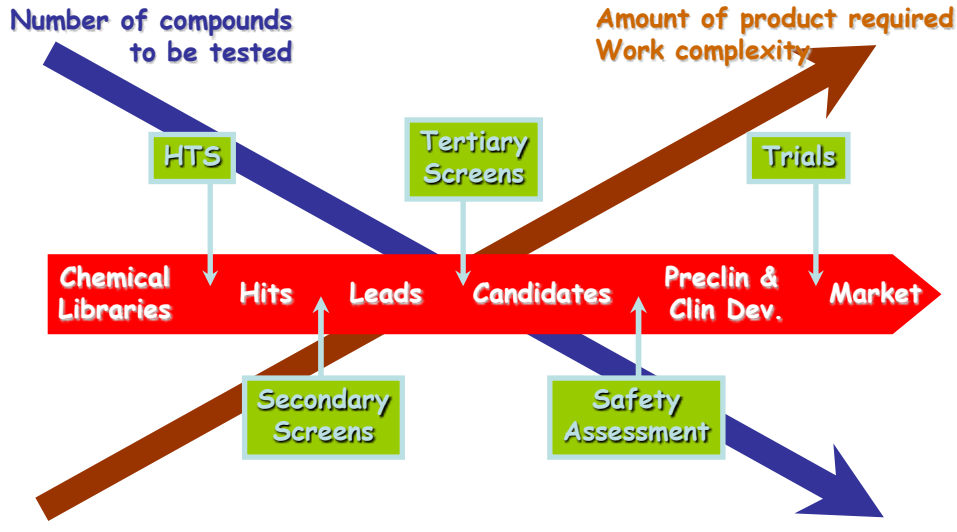
Maybe lower risks taken in clinical development?

LACK OF EFFICACY AND RISK ACCOUNT FOR MAJOR FAILURES IN DEVELOMENT

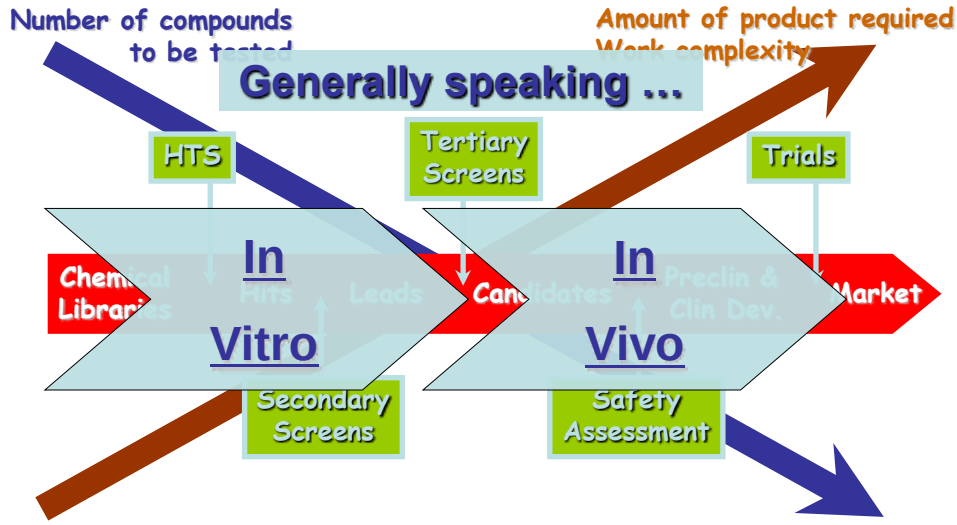


And this is happening despite the increasing economic efforts, the increasing safety requests from Authorities and the use of validated or non-validated assays…

INTRODUCTION (2)



INTRODUCTION (3)



DRUG INDUSTRIES NEED AND LIKE IN VITRO METHODS

1. ***In vitro*** **methods are cheap, fast, reproducible, easy to conduct, allow SAR evaluations, etc.**
2. **There are Regulatory Incentives to use *in vitro* approaches to safety assessment…**

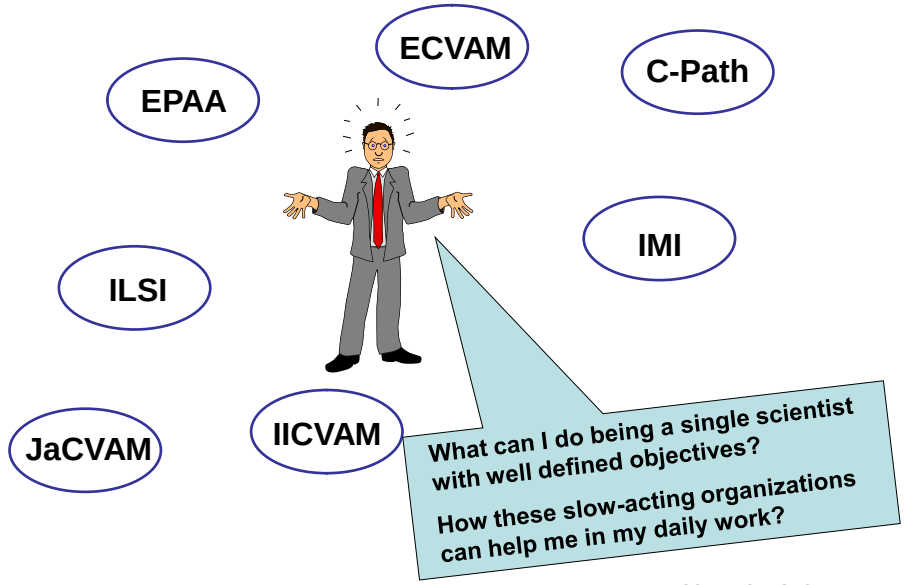
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Concept paper on the Need for Revision of the Position on the Replacement of Animal Studies by *in vitro* Models (CPMP/SWP/728/95)

1) Over the past years a shift has been observed towards the regulatory acceptance of scientifically valid in vitro methods as well as formally validated in vitro methods as part of an integrated testing strategy. Moreover focus has broadened to the application of all 3 R's, replacement, reduction and refinement, whilst historically much emphasis has been placed only on replacement of animal studies by one or more in vitro or in silico approaches. Large EU initiatives such as the European Centre for the Validation of Alternative Methods (ECVAM) and the European Partnership for Alternative Approaches to Animal Testing (EPAA) facilitate progress in this field. Finally, the application of all 3 R's is currently embedded the drafting process of non-clinical regulatory guidance both at EMA and ICH level.

2)

TOO MANY DRIVERS, POORLY CONNECTED



THREE OPEN QUESTIONS TODAY REGARDING POOR QUALITY OF IN VITRO APPROACHES

hERG: A test exists; its translation to risk in human is still difficult.

Genotoxicity testing: Experts have agreed, as reported in an ECVAM workshop, that genotoxicity tests in mammalian cells produce a remarkably and unacceptable occurrence of irrelevant positive results, as predictors of carcinogenicity

Photosafety testing: In vitro photosafety assays are substantially over predicting in vivo and human photosafety

THREE LEVELS OF VALIDATION

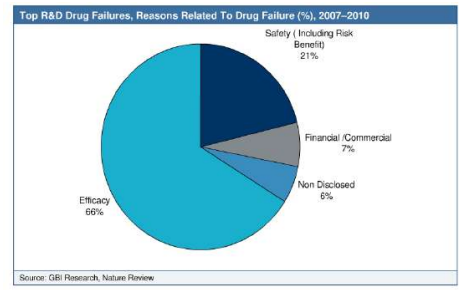
1. **INTERNAL VALIDATION:**
   - Assays/methods/models validated in house, helping in the decision making process.
2. **BY-USE VALIDATION:**
   - Assays/methods/models that are validated by its use by the scientific community.
3. **REGULATORY VALIDATION:**
   - Assays/methods/models properly validated following the defined guidelines.
   - These models may or may not be fully accepted by the final users.

THE LOTTERY ISSUE

1. Validations are based in correlations, algorithms, etc.
2. They never result in 100% concordance with what they want to predict (or mimic), then...
3. If my compounds are well predicted, I am happy…
4. If my compounds are not well predicted, I will eliminate good compounds or allow bad compounds to be developed. In this case, it does not matter the predictive value of a model: I AM DEVELOPING A BAD COMPOUND! (and my boss is unhappy!!!!).
5. And still, the pharma industry uses and develops many new *in vitro* methods to better select its candidates, aiming to improve safety and efficacy.

AND AGAIN… WE HHAVE UNDESIRABLE SURPRISES

1. Many of these failures are late surprises (Phase III and/or when in the market).
2. In many instances, lack of efficacy is associated to dose limits, depending on safety margins, which do not allow doses high enough to observe efficacy.



3. In many instances, lack of efficacy is associated to dose limits, depending on safety margins, which do not allow doses high enough to observe efficacy.
4. Many of the late surprises associated to safety include death or extreme situations.
5. COMPOUNDS FAIL IN “COMPLEX” SITUATIONS.

THUS, COMPLEXITY IS AN ISSUE

A CONCEPTUAL ERROR…? (or I like being conflictive!!!!!)

1. Reduction… OK!
2. Refinement… OK!
3. Replacement… A misleading concept!

- Replacement suggests test substitution…
- Replacement must be translated to a new way of conducting safety assessment in its totality… Can we reach the same conclusion regarding the risk assessment of a NCE by different means of the current approaches?

WE HAVE ACCEPTED THAT…

In vitro systems	*In vivo* systems
Fast	Slow
Less product	More product
Lower cost	Higher cost
Simple	Complex
Before	Later
(Non) Validated	Validated

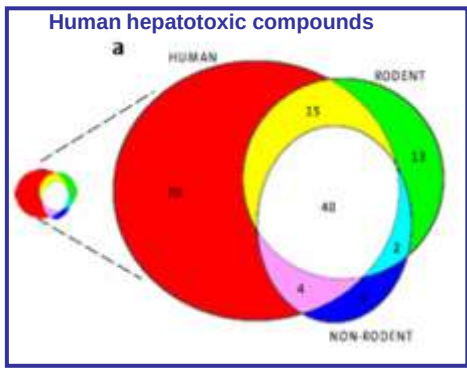
TO THINK AT HOME (1)

In vitro systems	*In vivo* systems
Fast	Slow
Less product	More product
	Higher cost
	Complex
	Later
	Validated

AChE inhibitors affect urinary bladder in dogs

Although in general they are good predictors of human safety, they also fail

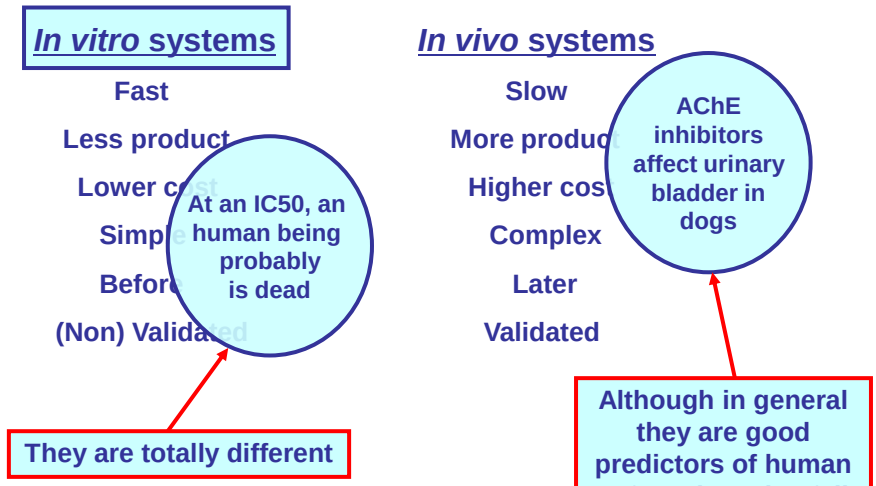
Human hepatotoxic compounds



Safety Inteligence Board Species Concordance

Steven Spanhaak, Chair of the EFPIA safety ad-hoc working group and principal scientist in toxicology at Johnson & Johnson PRD, Belgium

TO THINK AT HOME (2)



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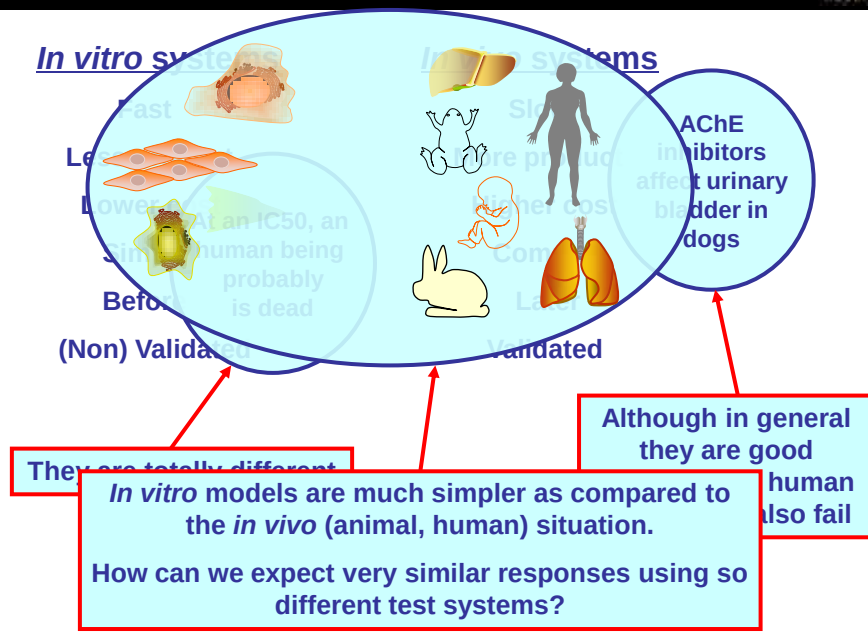


THE INDUSTRIAL PROPOSAL TO ACCELERATE VALIDATION (1)

- Modified from a Dr. S. Spanhaak presentation, Berlin, 2011

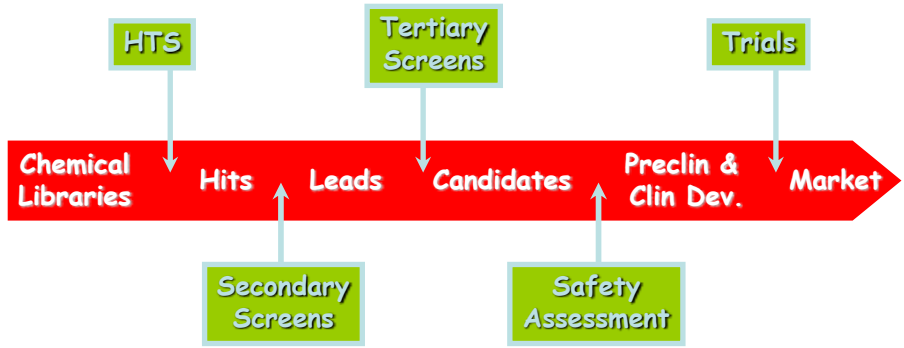
1. Validation is to be implemented within the ICH framework to accelerate the process
2. The validation process must be “global” to facilitate acceptance
3. Relevant parties must be involved:
   - Required: MHLV, FDA, EMA, JPMA, PhRMA, EFPIA
   - Observers: Health Canada, Swiss Medic, JaCVAM, ECVAM, ICCVAM, C-Path, EPAA, ILSI (why not ECOPA?).
4. Specific ICH meetings (peripheric to Safety meetings) for discussion
5. Interested parties (JaCVAM, ECVAM, ICCVAM, C-Path, EPAA, ILSI) propose a new assay or testing paradigm for inclusion in guidelines
6. First scientific discussion: Existing data and/or evidences regarding scientific and technical validity of the proposal..

THE INDUSTRIAL PROPOSAL TO ACCELERATE VALIDATION (2)

- Modified from a Dr. S. Spanhaak presentation, Berlin, 2011

7. Outcome:
   - Back to the lab
   - Real life evaluation under protection measures
   - Recommendation for regulatory implementation
8. ICH decides if new paradigm can be included in existing guidelines or if a new guideline must be developed
9. The protection measures:
   - Industry would conduct the new test/assay on a voluntary basis
   - Results would be submitted to Regulatory Authorities, but not used in any risk assessment (only data generation; to avoid the “hERG mistake”)
   - After evaluation of the results, assuming an appropriate testing period, the assay maybe rejected or accepted for regulatory application.

INDUSTRY REQUIRES NEW METHODS, BUT…



Momentum of the process

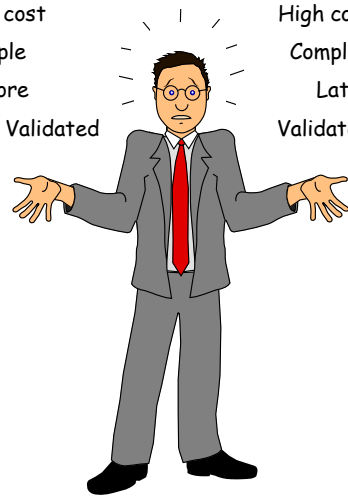
Cost of the assay, associated to momentum

Exclusion versus alerting

How make decisions? What to do after?

ANYHOW, THIS WILL BE A LONG PROCESS; UP TO YOU DECIDE WHAT TO DO!!!!!!!

Fast	Slow
Less product	More product
Low cost	High cost
Simple	Complex
Before	Later
Non Validated	Validated



Up to now, validation was considered as a Sisyphus never-ending work (Horst Spielmann)

LET'S TRY TO AVOID SISYPHUS IN OUR WORK!