



National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

New approaches in regulatory toxicology: why we need to change

Contemporary Concepts in Toxicology Webinar Series

18 June 2015

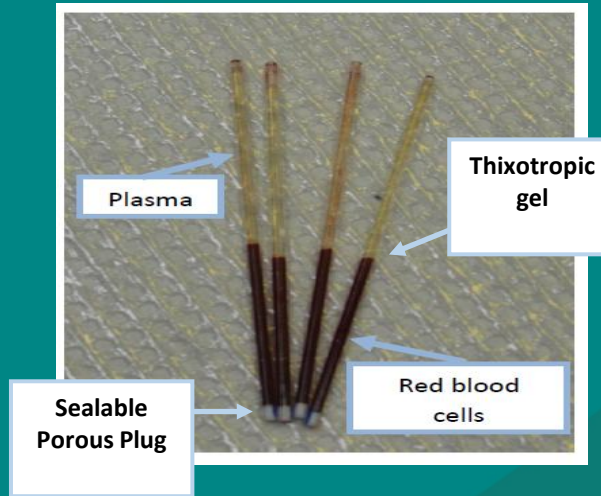
Kathryn Chapman, PhD

Background:

Current and future approaches in three areas:

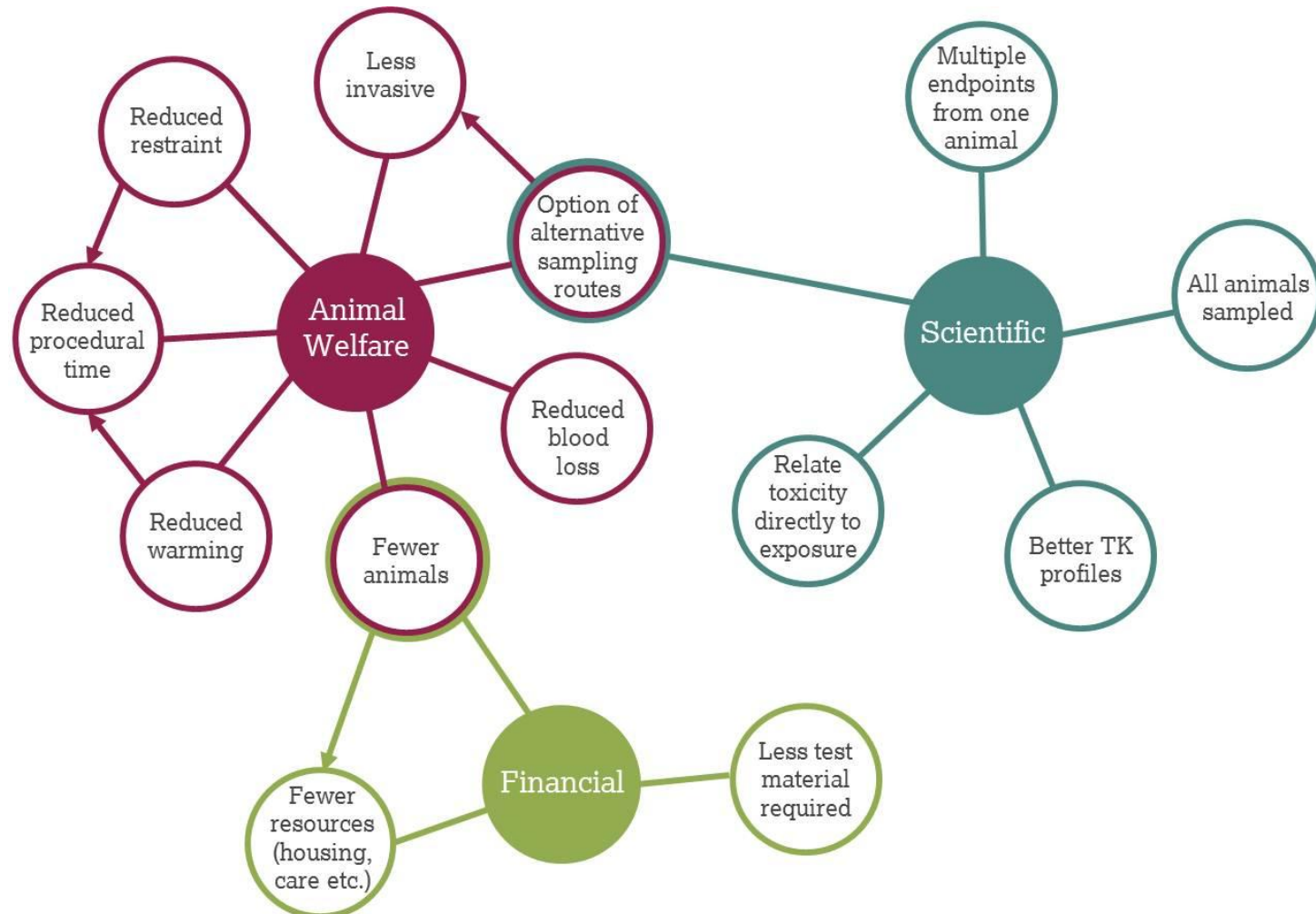
- Toxicokinetics and Microsampling
- CNS Safety Pharmacology
- Biosimilar Development

Toxicokinetics and Microsampling: An opportunity to improve science and reduce animal use



What is microsampling?

- A sample that is smaller than a 'normal' macrosample
- Can be a wet sample (plasma, serum or blood)
- Or a dried sample (spot on a card)
- Many benefits



Where are we now?

- Table 1: Conventional sampling from satellite animals

Dose group	Low	Medium	High	Control
No. animals	15M + 15F	15M + 15F	15M + 15F	15M + 15F
No. TK satellites	9M + 9F	9M + 9F	9M + 9F	9M + 9F
No. recovery			5M + 5F	5M + 5F
Maximum total for one study				Up to 200

- Table 2: Microsampling from satellite animals and smaller main size

Dose group	Low	Medium	High	Control
No. animals	15M + 15F	15M + 15F	15M + 15F	15M + 15F
No. TK satellites	3M + 3F	3M + 3F	3M + 3F	3M + 3F
No. recovery			5M + 5F	5M + 5F
Maximum total for one study				Up to 164

Where do we want to be?

- Table 3: Microsampling from main study animals

Dose group	Low	Medium	High	Control
No. animals	15M + 15F	15M + 15F	15M + 15F	15M + 15F
No. TK satellites	-	-	-	-
No. recovery			5M + 5F	5M + 5F
Maximum total for one study				Up to 140

Benefits:

- Refinements in sampling procedures e.g. reduced/no warming and reduced handling
- Uses fewer animals overall (save up to £130k/study)
- Sampling main study animals means the data can be directly linked to the observed toxicological effects in an individual animal
- Less drug/test item needed

Sampling sub-groups of animals? Default toxicokinetic sampling plan for 1-month study, all main study animals sampled.

A balanced study design with 10 animals/sex/group, composite TK with 6 time points and 3 samples per animal, 5 samples at all time points, 30 TK samples per group in total (previously 18 per group in total using satellite animals and serial sampling)

- Each animal has one sample from early, mid, late part of the curve

Animal No.	Sampling time point					
	#1	#2	#3	#4	#5	#6
1	x			x	x	
2	x			x		x
3		x		x	x	
4		x	x			x
5		x			x	x
6	x		x		x	
7	x		x			x
8	x		x	x		
9		x	x		x	
10		x		x		x
	n=5	n=5	n=5	n=5	n=5	n=5

Integrating microsampling into GLP regulatory toxicology studies through collaboration and data-sharing

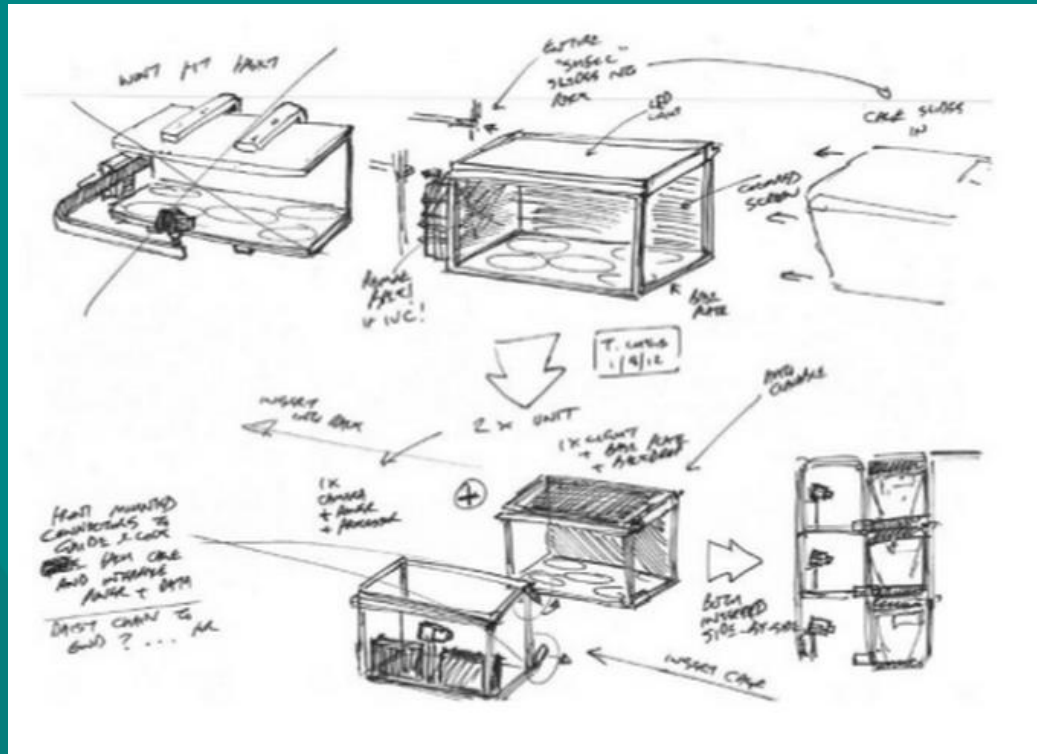
- Microsampling user group and workshops with 33 companies to share wider experience and explore the barriers to uptake of microsampling

	Barrier 1	Barrier 2
	<p>Regulatory acceptance</p> <ul style="list-style-type: none"> - Definition of a microsample - Use of main study animals may interfere with study outcome 	<p>Practical acceptance</p> <ul style="list-style-type: none"> - Knowledge and experience of sampling techniques - Change in infrastructure and practice needed
Approach	<ul style="list-style-type: none"> - Agreed definition for microsample - Link exposure to observed toxicity - Shared data and experience on impact on clinical pathology (Glover <i>et al</i>) - Liaise with regulators 	<ul style="list-style-type: none"> - Shared practical 'hints and tips' - Developing a web-based portal (video etc.) - Microsampling user group (42 scientists from 25 companies)
	Peer reviewed cross-company publications	
Impact	<ul style="list-style-type: none"> - Input into regulatory change (ICH S3 Q&A) 	<ul style="list-style-type: none"> - Reduction of the number of rats (200 to 140/study) and mice (158 to 80) - Refinement (less warming and handling)

- **IMPACT:** Less compound, reduced costs, better science, fewer animals, better welfare

Consensus definition: A microsample may be defined as a small volume of blood which would allow serial or composite sampling of main study animals with limited impact on other study parameters. Typically a normal sample would be ~200ul (range 100-800ul) and a microsample 25-50ul (range 10-100ul).

CNS Safety Pharmacology: Animals are not always telling us what we think they are



Predictive capacity of animal models

- 1. Review the current models
- 2. Cross-company data-sharing
- 3. Is change needed?



CNS Safety Pharmacology

6 companies, 141 compounds (24% of total Phase 1)

Small molecules only (nonclinical vs clinical data)

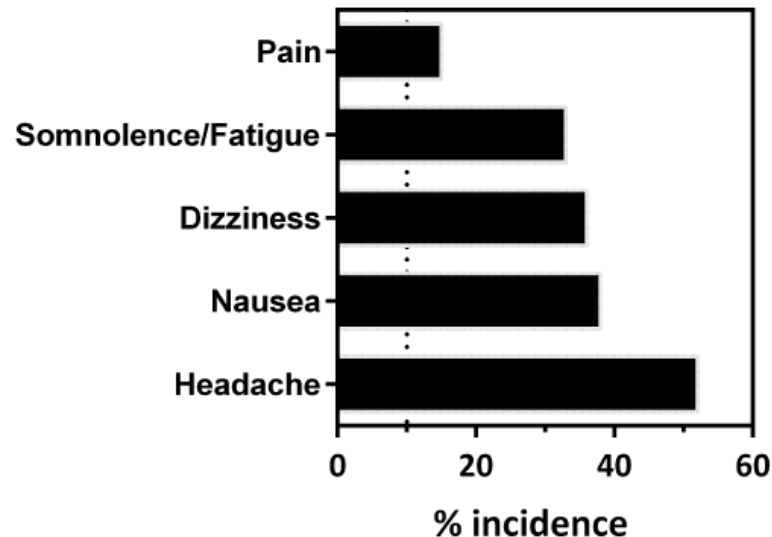
Nonclinical (rodent)	Clinical
Functional Observational Battery IRWIN Increase/decrease in food consumption	Phase 1 clinical trials adverse events
Dose and exposure	Dose and exposure (inc. free Cmax)

Predictive capacity of CNS safety pharmacology models

- 62% of compounds were non-CNS targets (38% CNS)
- Analysed top 5 commonly observed adverse effects observed in Phase 1 clinical trials
- 90% of CNS-targeted drugs had reported AEs, 68% non-CNS

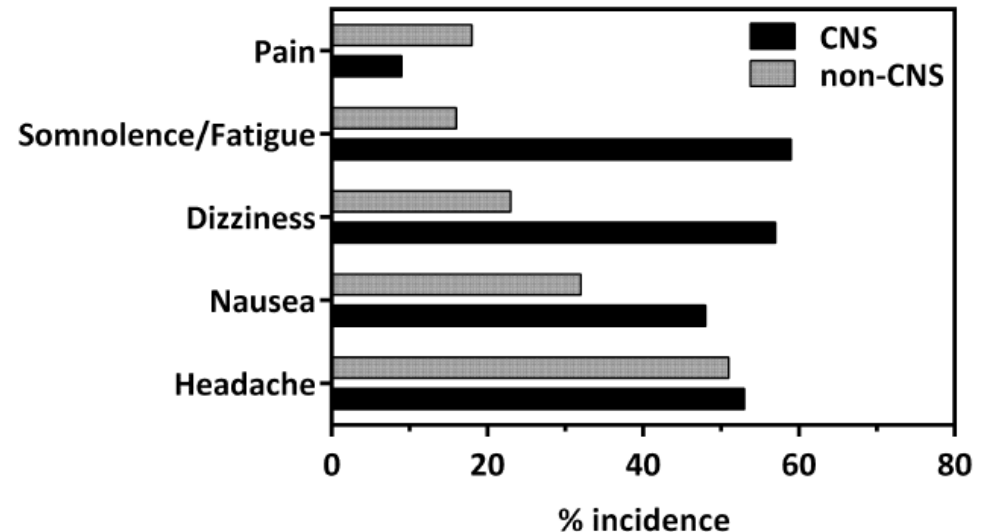
A

Incidence of Clinical AE's



B

Incidence of Clinical AE's: CNS vs non-CNS targeted compounds



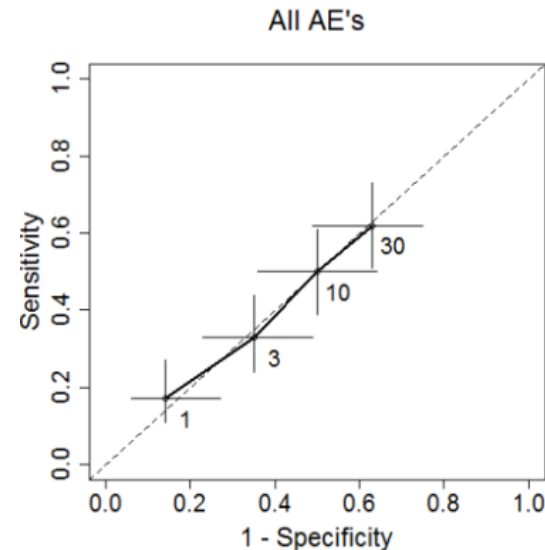
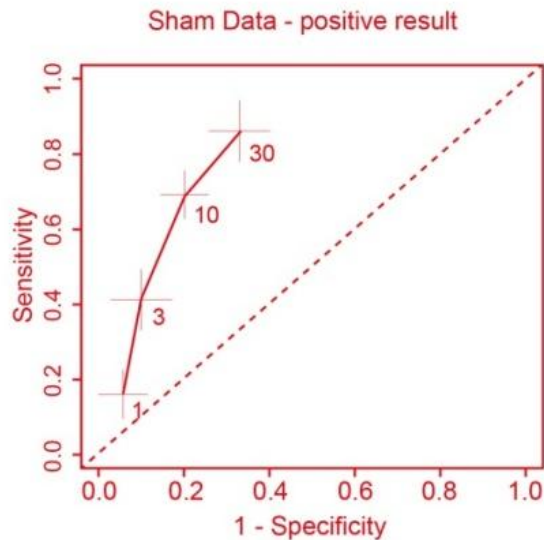
CNS safety pharmacology models – 2 analyses

- Overt toxicity analysis: any nonclinical AE vs any clinical AE
- Plausible correlate analysis: related nonclinical vs clinical

Clinical AE	Nonclinical Plausible Correlates
Headache	None
Nausea	Decreased body weight gain or decreased food consumption.
Dizziness	Decreased horizontal locomotor activity, decreased rearing (automated) or decreased rearing (observer scored)
Somnolence/ Fatigue	Decreased home cage arousal or decreased grip strength or decreased handling reactivity or increased hunched posture or decreased horizontal activity (automated) or decreased rearing (automated) or decreased rearing (observer scored)
Pain	Decreased horizontal locomotor activity, decreased rearing (automated) or decreased rearing (observer scored) or increased vocalization.

Data analysis (1)

- Overt toxicity analysis
- Occurrence of a nonclinical AE does not predict a clinical AE
- This also holds true when stratified into CNS-targeted and peripherally-targeted molecules

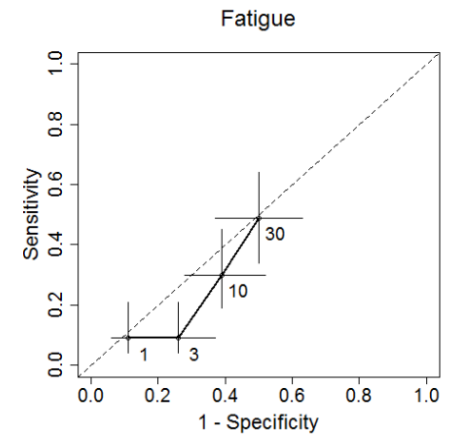
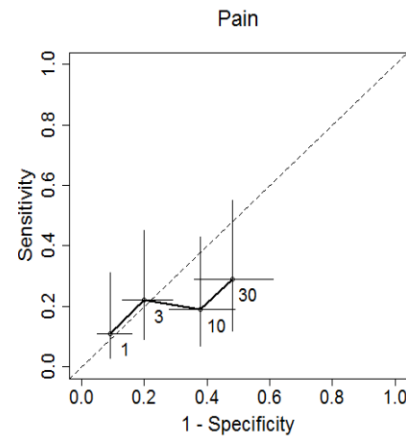
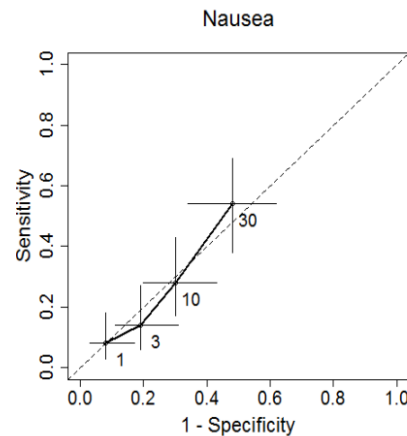
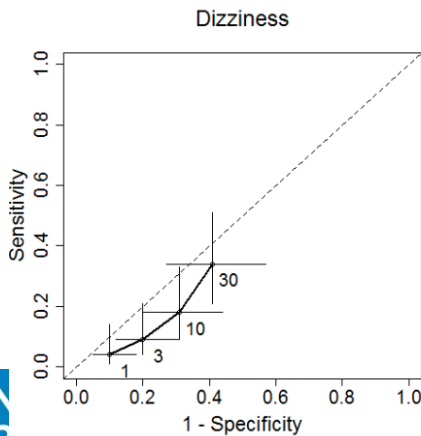
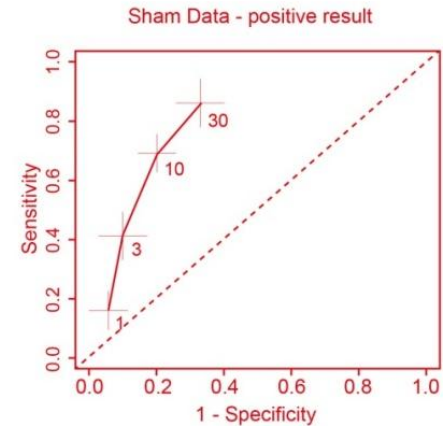


Parameter	Formula
Accuracy	$(TP+TN)/(TP+TN+FP+FN)$
Sensitivity	$TP/(TP+FN)$
Specificity	$TN/(TN+FP)$
Positive Predictive Value (PPV)	$(SENS*PREV)/(SENS*PREV+(1-SPEC)*(1-PREV))$
Negative Predictive Value (NPV)	$SPEC*(1-PREV)/(SPEC*(1-PREV)+(1-SENS)*(PREV))$

Data analysis (2)

- Plausible correlate analysis
- Occurrence of a nonclinical AE does not predict a clinical AE
- Lack of prediction may contribute to attrition

E.g. Fatigue – preclinical correlates: reduced home cage arousal, reduced activity, reduced handling reactivity



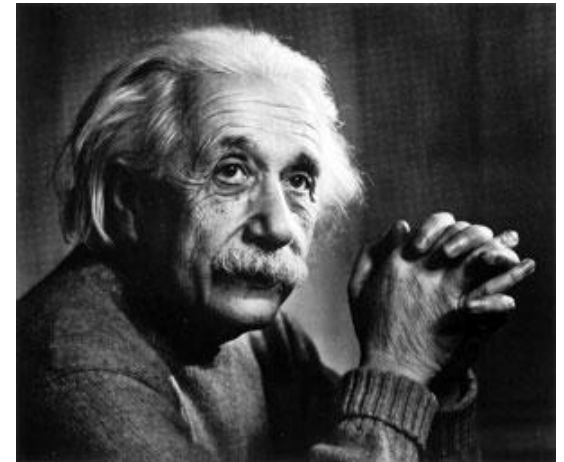
Predictive capacity of CNS safety pharmacology models - conclusion

- The rodent neurofunctional assessment should not be used to reliably predict the occurrence of the most commonly-observed AEs in FIH studies.
- Start not the end



CRACK IT
Technologies for better science

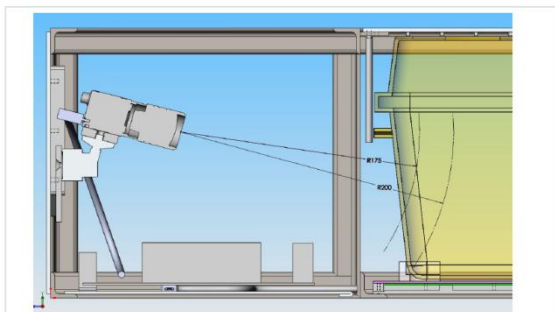
“If I had only one hour to save the world, I would spend fifty-five minutes defining the problem, and only five minutes finding the solution.”



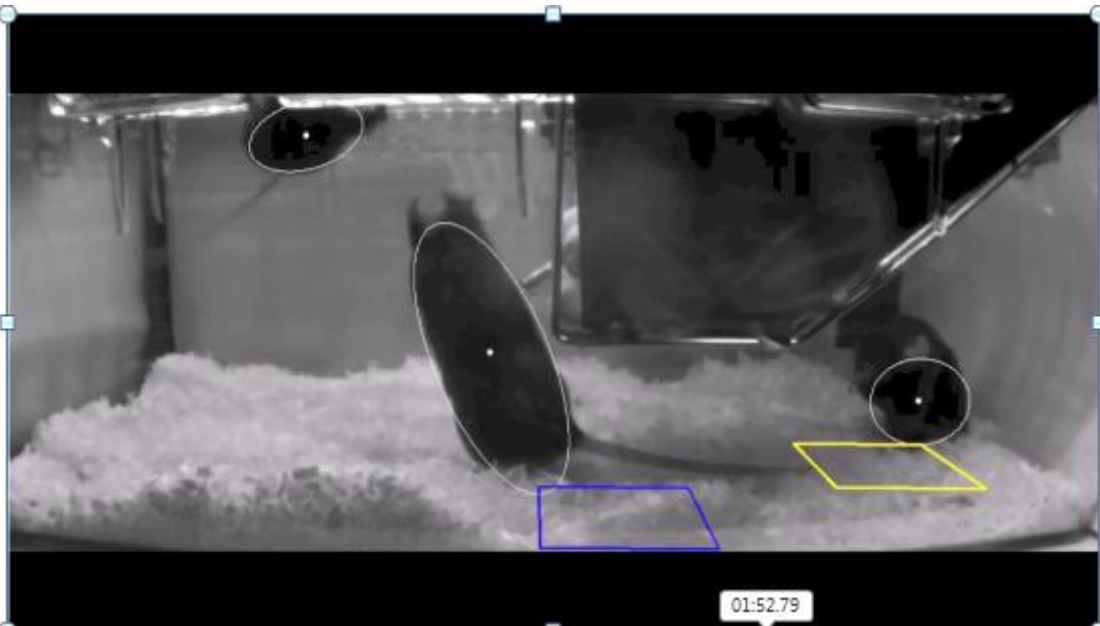
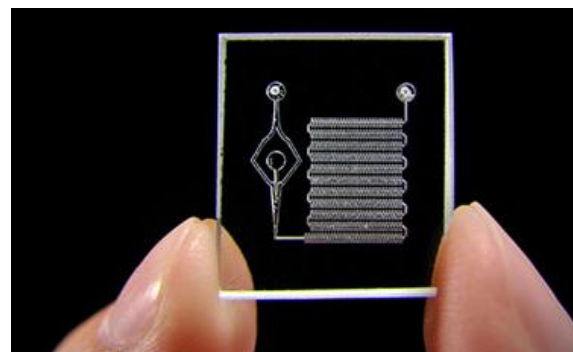
Identified and defined the problem so what next?

- Get more and better data from different more predictive animal studies

Mechanical update, camera stand off



- Use non-animal technologies



SANOFI

gsk do more feel better live longer

Challenge 17: Neuratec

Launch Meeting
12 September 2014

abbvie

BASF
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Biosimilar Development: Global regulatory environment can drive unnecessary use of animals

Biosimilars: Shorter Path to Approval

Looking to rein in spiraling medical costs, the FDA wants to facilitate the approval process for biosimilars. But the complexity of biosimilars will provide manufacturers with increased pricing power and larger margins compared to traditional generics.



2011



**Current
Biosimilars
Market
Value:**
**\$400
million**
(approximate)

Source: IMS Health

2020



**Potential
Revenues
from
Biosimilars
Sales:**
**\$11-25
billion**

What are biosimilars?

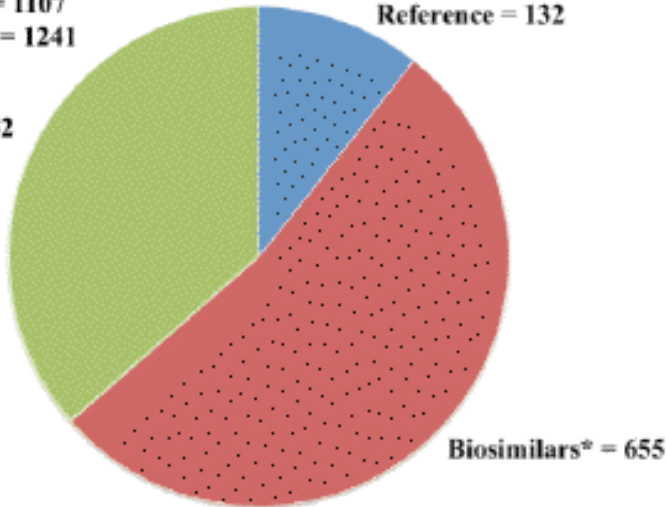
- 'Generic' protein and antibody-based drugs
- Cheaper and affordable therapies for cancer and immune diseases
- Global markets
- Companies need to show that the new product is 'similar' to the original so-called biosimilar
- Non-human primates often the only relevant species



Biosimilar development is increasing

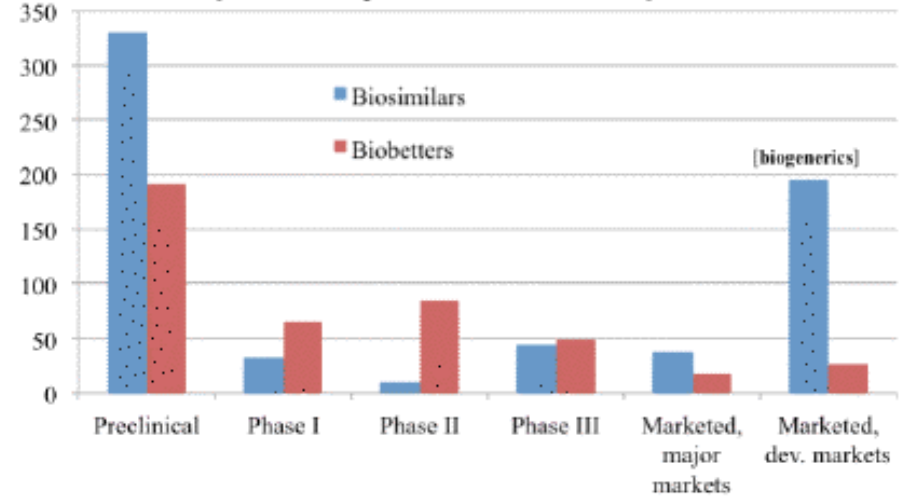
Total pipeline = 1107
Total products = 1241

Biobetters = 452

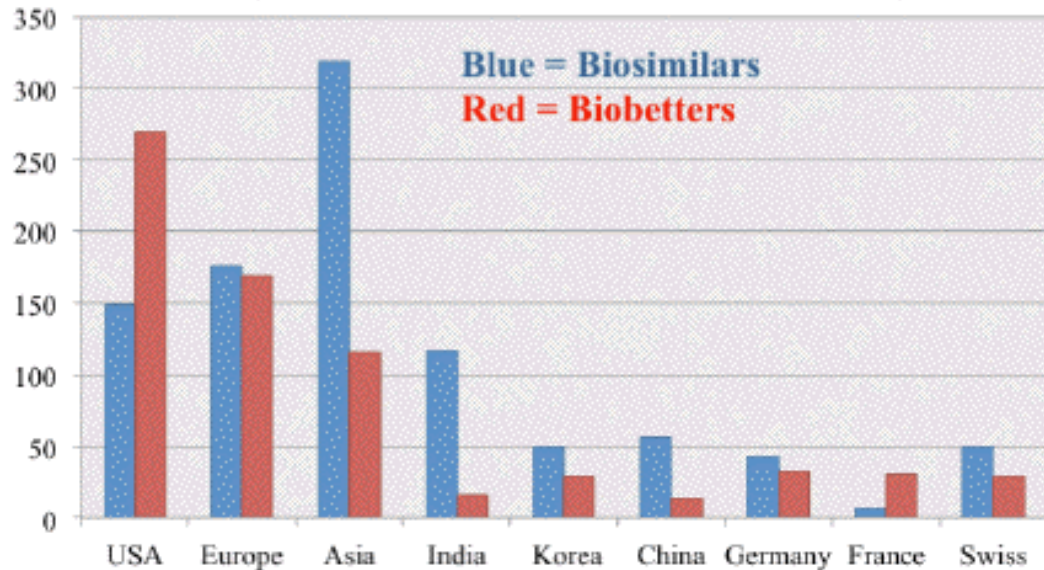


*Biogenics in international commerce are included as biosimilars.

Pipelines By Phase of Development



Regions/Countries by No. of Products



Biosimilar development – are we being driven by science?

Typical study design for a comparative toxicology study for a mAb biosimilar

- Control and 3 dose levels
- Recovery group in control and HD groups
- Biosimilar and ref material (s)
- 3/sex/group and 2/sex/group recovery
- 60 animals – generally NHPs for mAb products

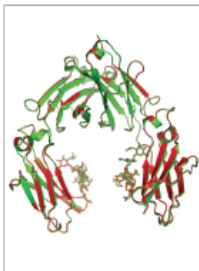
Plus

- PK bioequivalence study with 12-16 NHPs per group
- **Total: > 84 animals** depending on number of reference materials used as comparators

EMA guidance suggests *in vitro* only

mAbs
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Editor-in-Chief
James M. Beckwith



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Biosimilars entering the clinic without animal studies

Leon AGJM van Aerts^{abc}, Karen De Smet^{def}, Gabriele Reichmann^{ceg}, Jan Willem van der Laan^{ah} & Christian K Schneider^{ij}

^a Medicines Evaluation Board (CBG-MEB); Utrecht, Netherlands

^b Member of the Safety Working Party (SWP); EMA; London, UK

^c Expert of
Committee

^d Federal A

^e Expert of

^f Member of

^g Paul Ehrli

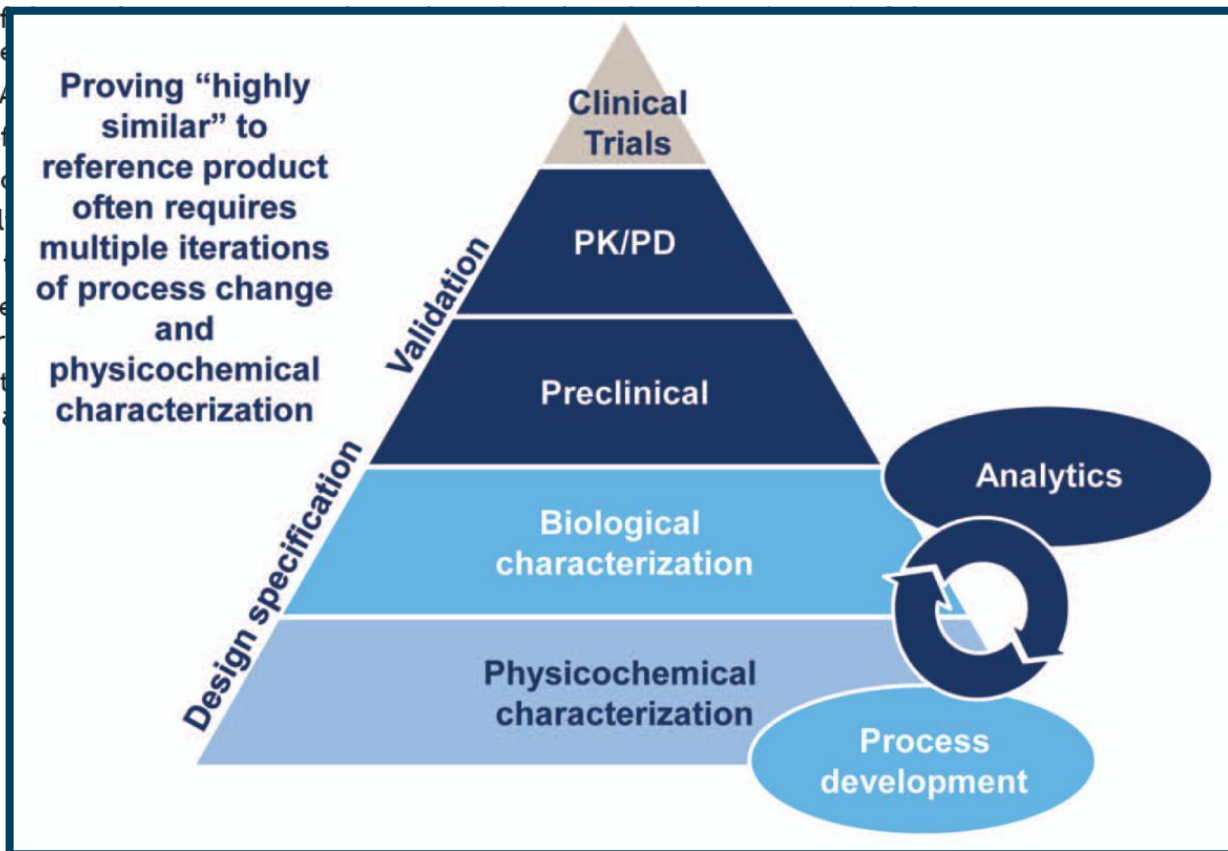
^h Chair of

ⁱ Danish He

Centre for

^j Chair of t

Accepted a



NC3Rs/MHRA Biosimilar working group

- Joint initiative between the MHRA and the NC3Rs
- 12 companies from UK, Europe, US, Korea, Japan, Russia, India, Canada
- 4 regulatory bodies (national and international)
- Shared data from 26 products

Companies With the Largest Biosimilars and Biobetters Pipelines

Biosimilars (10 or more)

Harvest Moon Pharmaceuticals USA, Inc.	28
BioXpress Therapeutics S.A.	19
Zydus Cadilla Healthcare Ltd.	17
Biocon Ltd.	17
Mylan Labs.	14
Inbiopro Solutions Pvt Ltd.	14
Creative Biomart Inc.	13
Green Cross Corp.	12
Bio Sidus S.A.	12
AXXO GmbH	12
Dong-A Pharmaceutical.	12
Bioton S.A.	11
Chemo Group (Grupo Insud)	11
Novartis AG	10
LG Life Sciences Ltd.	10
Amega Biotech	10
Cassara Biotech	10

No company had experience of *in vitro* data alone being accepted for a biosimilar mAb

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This is even when the same *in vitro* assays as for the original product were used and there were no differences detected

Current Approach – where we are now?

- For all products at least one *in vivo* study was carried out
- 75% non-human primate, 25% rat
- Most (14/26) are 4 weeks in duration with some single dose studies and durations up to 26 weeks
- Most NHP studies are 3M+3F/dose but some are up to 5M+5F
- Most rodent studies are 10M+10F/dose but some are up to 15M+15F (Range: 3-15)
- For 3 products a DART study had been requested in non-human primates

Future Approach – where do we want to be?

- All companies agree *in vitro* studies are more sensitive to pick up differences than *in vivo*
- All companies agree that where *in vivo* studies may add value a minimised study design (n=20) would suffice
- All companies had carried out or were asked to carry out *in vivo* studies that they did not consider to add scientific value
- One company was asked to carry out an NHP and a rodent study with the biosimilar when the clinical molecule had not been tested in these species (relevant in chimp and human only)
- Do we need to use as many non-human primates as we currently are?

Why the 3Rs? Better science, business and welfare

- Reopen and input into WHO guidance
- National practice and guidelines (China - - - -)
- Global harmonisation
- Recommendations include:
 - *in vitro* only
 - minimised *in vivo*
- Clarify the **scientific** reason for the studies: they are not to assess safety but to detect differences between products



UNOFFICIAL ENGLISH TRANSLATION
Guidelines for R&D and Evaluation Techniques of
Biosimilars

(Exposure Draft)

Centre for Drug Evaluation, SFDA

October 29, 2014

New approaches in regulatory toxicology: why we need to change?

- Opportunities exist to do better science
- Animals are not always telling us what we think they are – may be better approaches in the future
- Global regulatory environment can drive unnecessary use of animals



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Get in touch

- Email: kathryn.chapman@nc3rs.org.uk
- Website: www.nc3rs.org.uk and www.crackit.org.uk
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