To what extent are challenge agents acceptable?

…challenges in early clinical drug development…

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22 May 2015

How acceptable are challenge agents?

content

- Challenge agents: why and what?
- Case study
- Legal considerations
- Ethical considerations
- Conclusion

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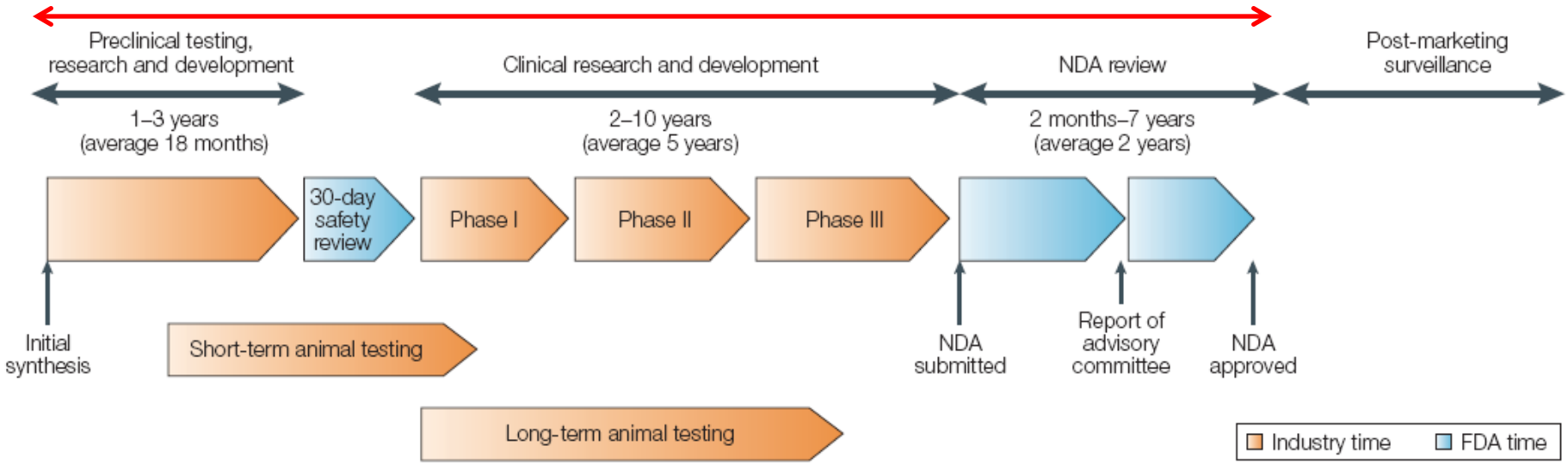
How acceptable are challenge agents?

why? (1)



Nat Rev Drug Disc 2004; 3: 417-429

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How acceptable are challenge agents?

why? (2)

Research Spending Per New Drug

Fosters, March 2012

Company	Ticker	Number of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca	AZN	5	11,790.93	58,955
GlaxoSmithKline	GSK	10	8,170.81	81,708
Sanofi	SNY	8	7,909.26	63,274
Roche Holding AG	RHHBY	11	7,803.77	85,841
Pfizer Inc.	PFE	14	7,727.03	108,178

How acceptable are challenge agents?

why? (3)

Johnson & Johnson	JNJ	15	5,885.65	88,285
Eli Lilly & Co.	LLY	11	4,577.04	50,347
Abbott Laboratories	ABT	8	4,496.21	35,970
Merck & Co Inc	MRK	16	4,209.99	67,360
Bristol-Myers Squibb Co.	BMY	11	4,152.26	45,675
Novartis AG	NVS	21	3,983.13	83,646
Amgen Inc.	AMGN	9	3,692.14	33,229

Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems

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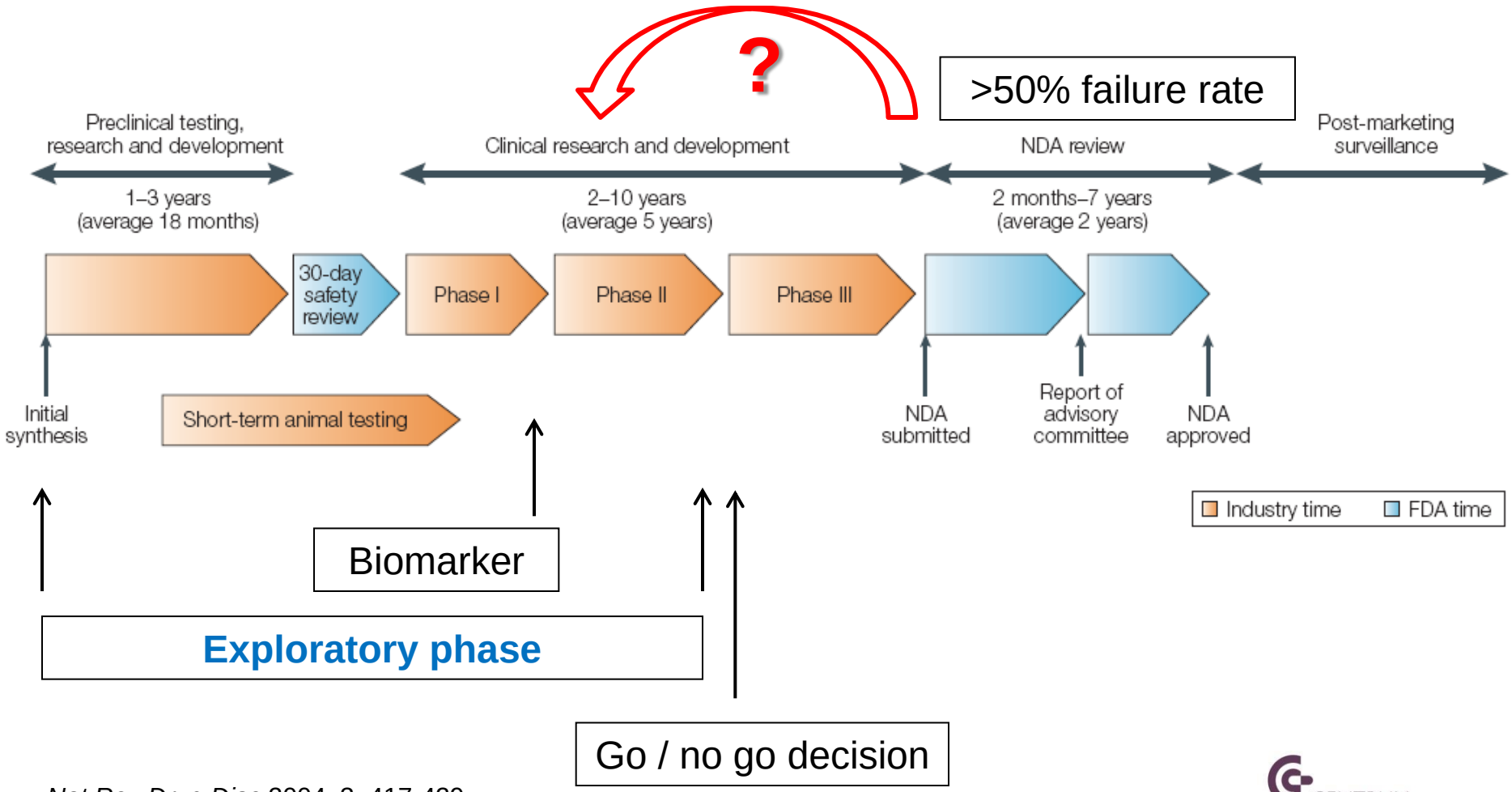
How acceptable are challenge agents?

why? (4)



Nat Rev Drug Disc 2004; 3: 417-429

How acceptable are challenge agents?

what? (1)

Biomarker:

An objectively measured characteristic as an indicator of: normal process, a pathological process, a pharmacological response to a (therapeutic) intervention or … *a physiological response to a (non-therapeutic) intervention*.

Challenge agent:

Substance inducing a (patho)physiological response to assess the pharmacological action of an IMP.

Annu Rev Pharmacol Toxicol 2008; 48: 631-51

How acceptable are challenge agents?

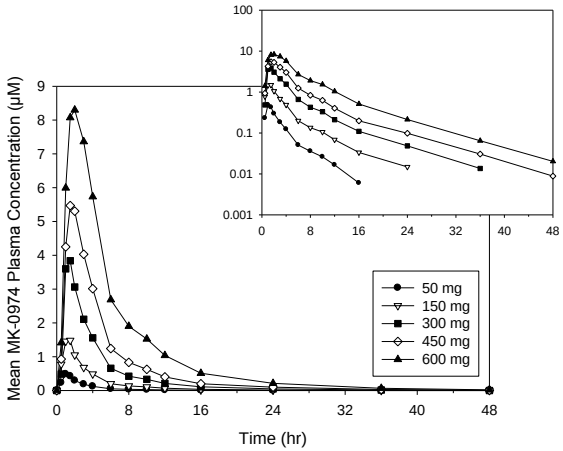
what? (2)

Challenge agent	Activity	Route of administration
allergens	allergic reaction	skin prick / inhalation
acetylcholine	M-receptor agonist	inhalation / IA
histamine	H1- H2 agonist	skin prick / IA
isoprenaline	β-receptor agonist	IV
substance P	NK-receptor agonist	skin prick / IV / IA
serotonin	5-HT agonist	IV / IA
P450 probes	CYP450 phenotypes	oral

(Based on ABPI Guideline for phase 1 clinical trials, edition 2012)

How acceptable are challenge agents?

case study



DOSE

↓

plasma concentration

↓

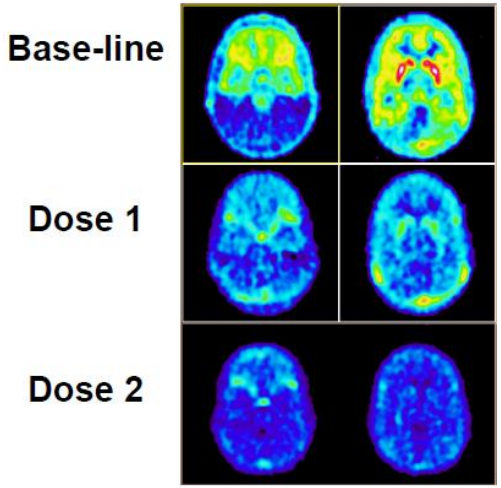
target tissue concentration

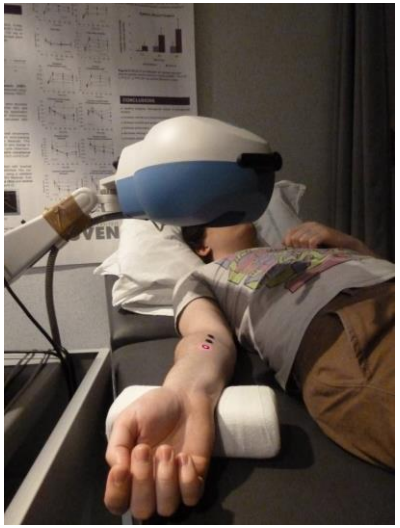
↓

target "receptor" concentration

↓

RESPONSE





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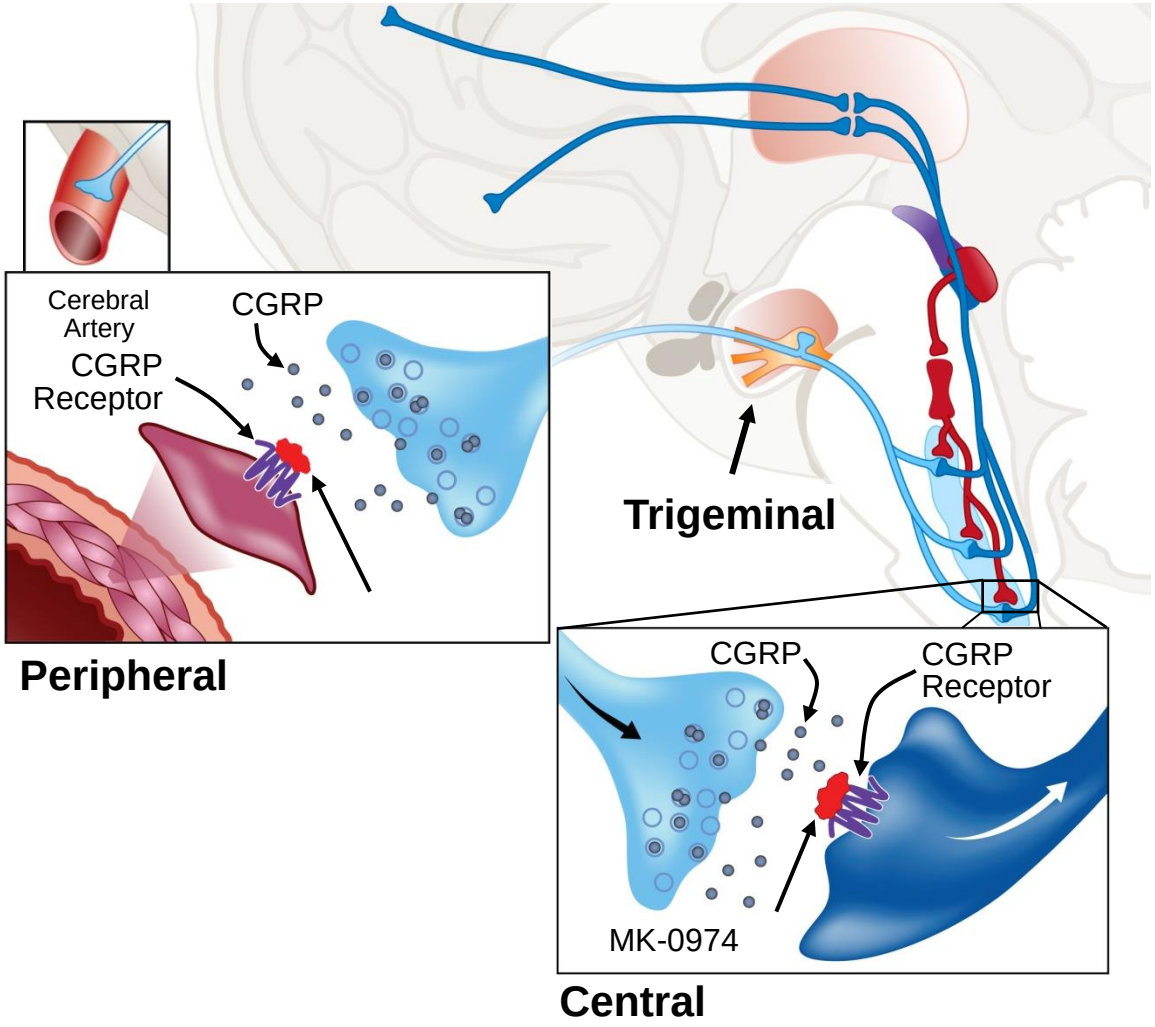
How acceptable are challenge agents?

case study: migraine



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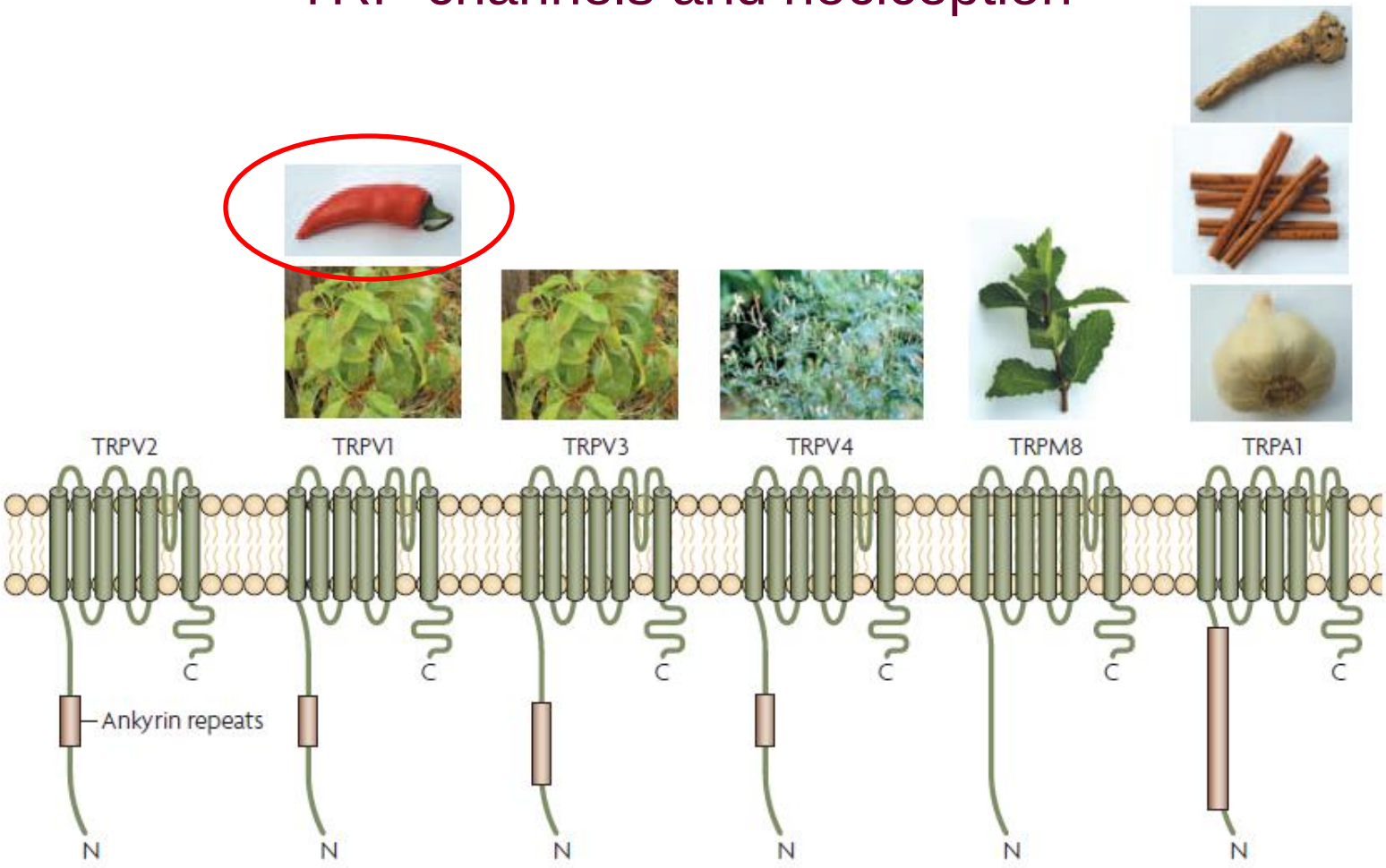
How acceptable are challenge agents?

TRP channels and nociception



Nature Drug Rev Disc 2007; 6, 357-372

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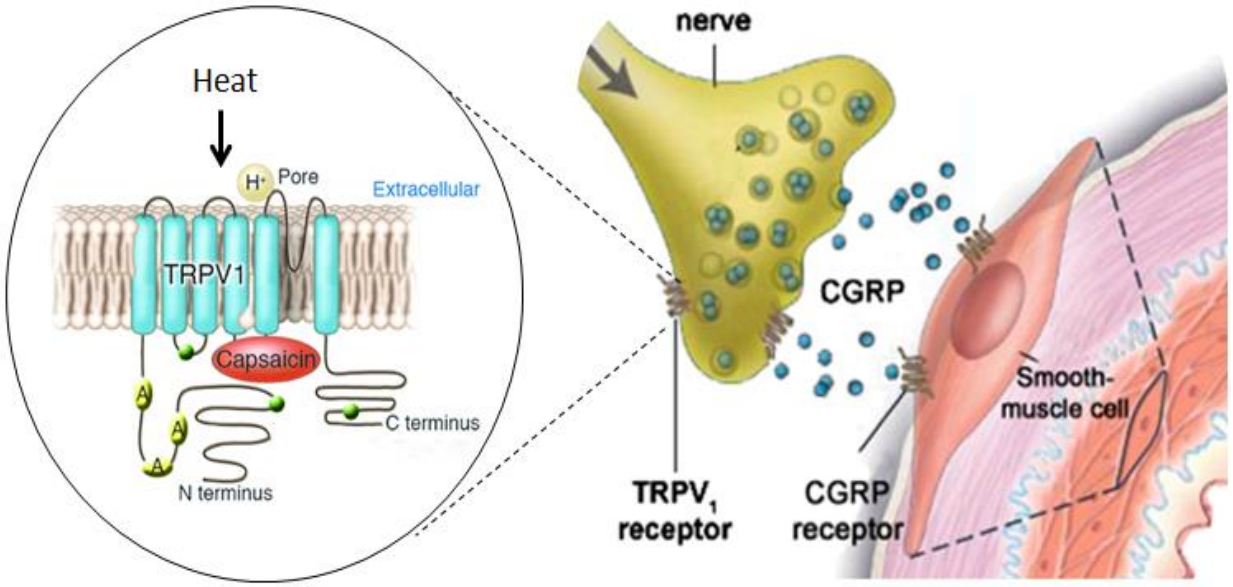
How acceptable are challenge agents?

capsaicin-induced CGRP release: the principle



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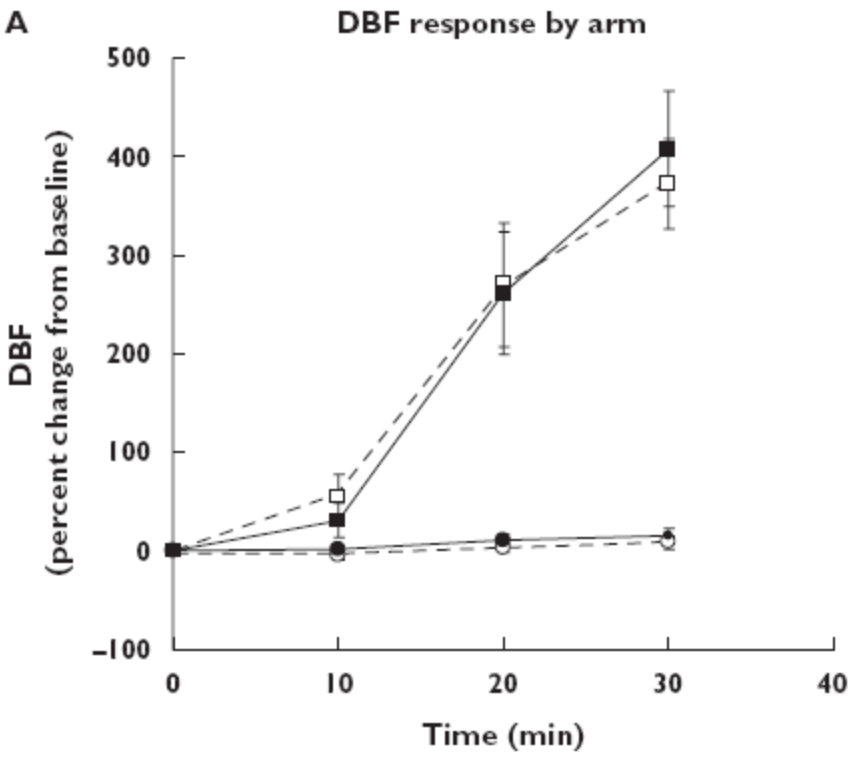
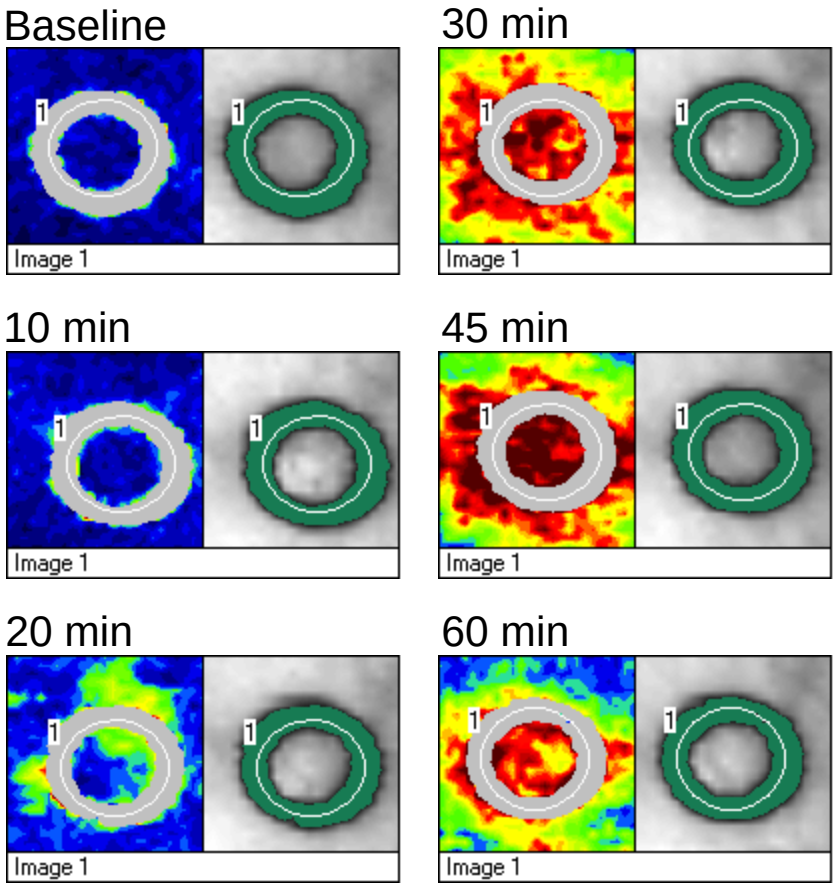
How acceptable are challenge agents?

capsaicin-induced CGRP release in HP





Van der Schueren et al. *Br J Clin Pharmacol* 2007; 64: 580-590

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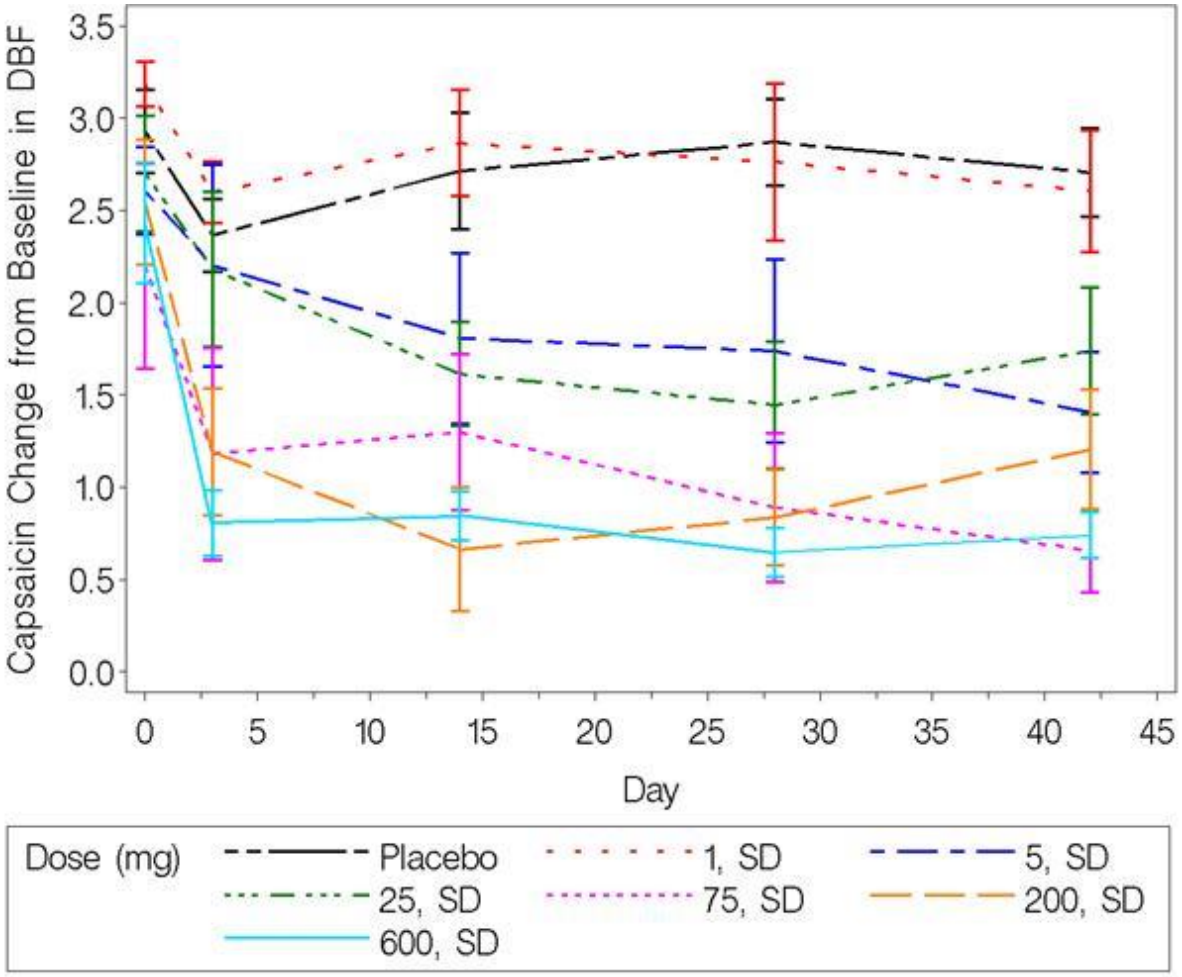
How acceptable are challenge agents?

CGRP binding mAb: LY2951742



J. de Hoon et al., *Cephalalgia* 2013; vol 33(8 Suppl): 247-248, P367; (IHC Boston, 2013)

S. Vermeersch et al., *Cephalalgia* 2013; vol 33(8 Suppl): 249-250, P370; (IHC Boston, 2013)

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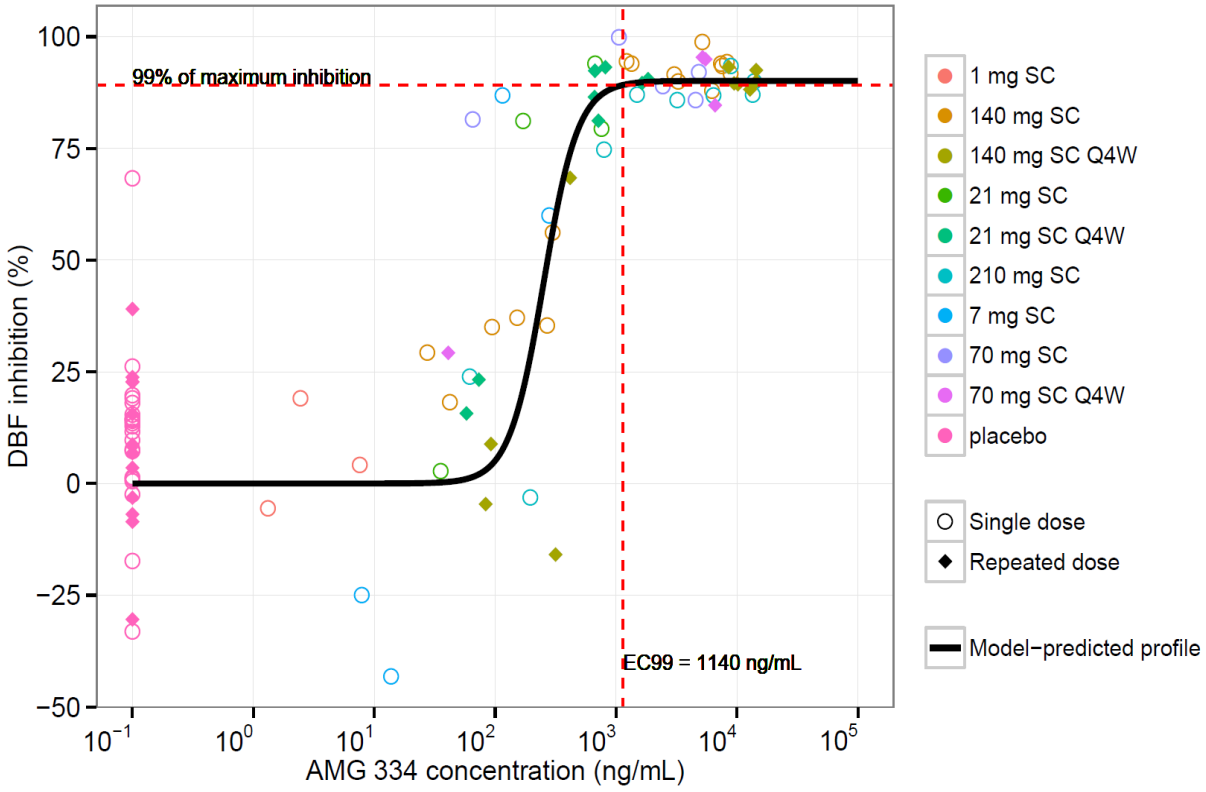
How acceptable are challenge agents?

CGRP-R binding mAb: AMG 334



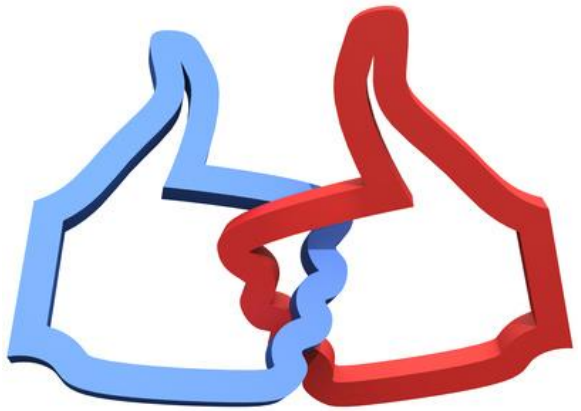
T. Vu et al., *International Headache Conference,* Valencia, May 2015

How acceptable are challenge agents?

to what extent are challenge agents acceptable?

Would you consider these challenge agents acceptable?

- **Legal considerations**:
  - safety / toxicology
  - quality
- **Complicating factors:**
  - purpose
  - route
  - species
  - dose
- **Ethical considerations**:
  - tolerability
  - reversibility



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How acceptable are challenge agents?
legal considerations (1)

- Legal status of a challenge agent?
  - *“medicinal product (MP) intended for research & development trials” …*

    which may or may not have a marketing authorisation.
  - “non-investigational medicinal product” (NIMP / auxiliary MP):
    - ~~Rescue medication~~
    - Challenge agents
    - ~~Products to assess~~ end-points (e.g. PET)
    - Concomitant medication
    - Background treatment

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION
VOLUME 10 - GUIDANCE DOCUMENTS APPLYING TO CLINICAL TRIALS
GUIDANCE ON INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS) AND 'NON INVESTIGATIONAL MEDICINAL PRODUCTS' (NIMPS)
(REV. 1, MARCH 2011)

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How acceptable are challenge agents?
legal considerations (2)

- Requirements for NIMP?
  - "*Manufacturing of NIMPs does not fall within the rules for manufacturing of MP*", therefore GMP is not a requirement, however…
  - "*…the sponsor should ensure the same level of quality and safety for NIMPs as for the IMPs used in the trials…this requirement will be fulfilled by applying for these NIMPs the same requirements as provided for the IMPs…*"
  - Possibility for a *"simplified dossier"…*
  - (Dose dependent: option for microdosing and exploratory approach)

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How acceptable are challenge agents?

challenge agents: an IMP in disguise

OPINION

The risks of risk aversion in drug regulation

Nature Drug Rev Disc 2013; 12: 907-916

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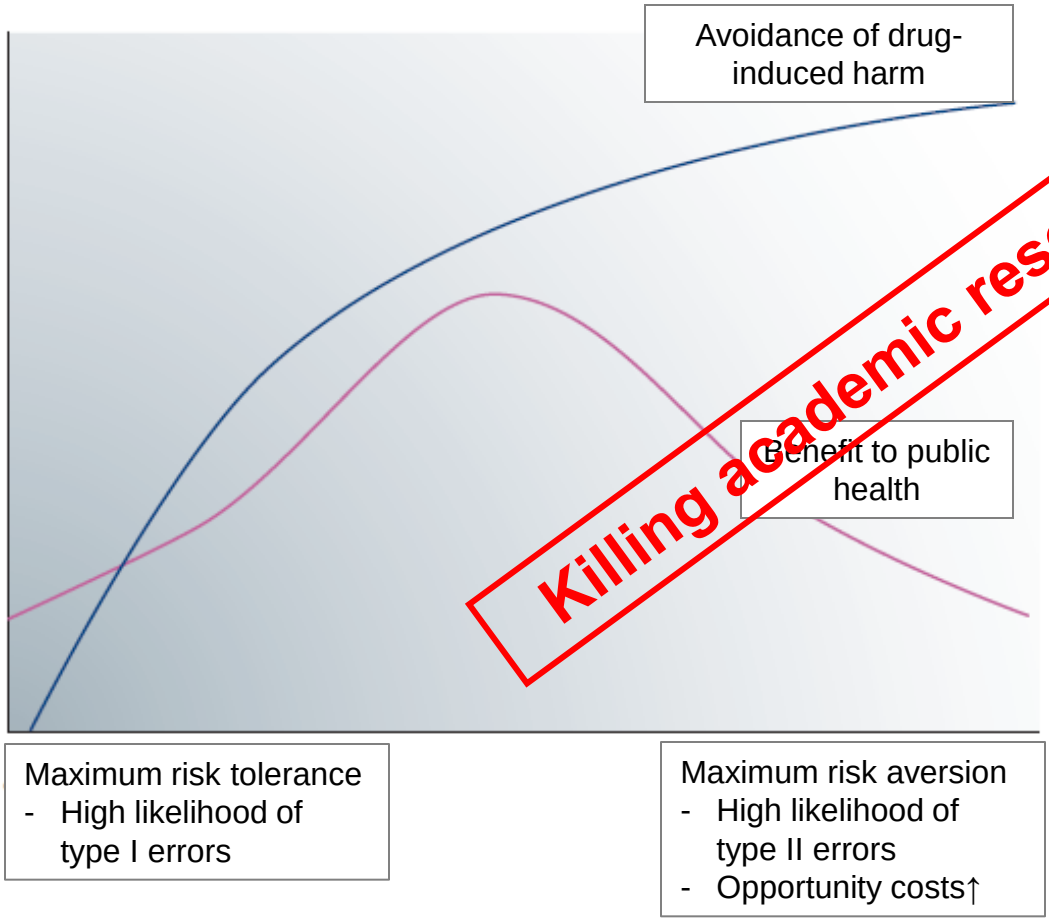
How acceptable are challenge agents?

"efficiency function" in drug regulation



Nature Drug Rev Disc 2013; 12: 907-916

How much risk is acceptable?

- Excessive risk-tolerance: unsafe and ineffective drugs
- Hippocrates:"*First, do no harm*": loss of useful drugs
- Acceptability and context:
  - healthy volunteer
  - patient
  - child …
- Room for uncertainty:
  - accept harm versus "zero tolerance"
  - information → opportunity costs

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OPINION

The risks of risk aversion in drug regulation

Nature Drug Rev Disc 2013; 12: 907-916

"… risk aversion comes with its own risks. Stakeholders should be aware that a drive towards an excessive focus on avoiding risks and uncertainties will mean that patients pay a price: delay in accessing therapeutics and lost therapeutic options."

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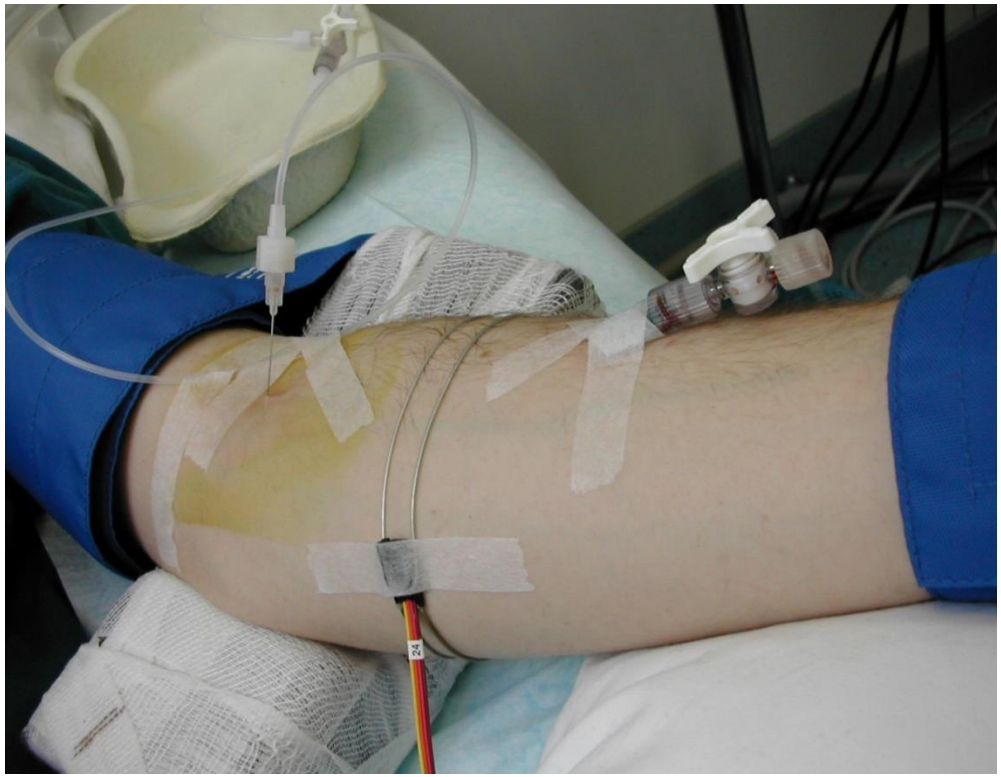
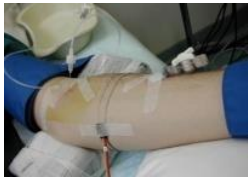
How acceptable are challenge agents?
complicating factors (1)



- **Route of administration?**
  - parenteral: IA or IV
  - sterility!
  - clean room
  - costs …
- **Species?**
  - HP versus others
  - "*not for human use*"



de Hoon et al. *Clin Pharmacol Ther* 2003; 73: 312-321
Vanmolkot et al. *Clin Pharmacol Ther* 2006; 79: 263-73

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How acceptable are challenge agents?
complicating factors (2)

Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura

Jakob Møller Hansen, Anne Werner Hauge, Jes Olesen and Messoud Ashina

Cephalalgia 2010; 30: 1179-1186

Table 2. MA patients and controls reporting headache and migraine-like attacks after CGRP*

Attack	MA patients	Controls	*p* value
Migraine-like attacks (post-infusion phase 1–13 hours)	8/14	0/11	.003
Headache (infusion phase 0–60 min)	11/14	7/11	.65
Headache (post-infusion phase 1–13 hours)	12/14	2/11	.001

MA = migraine with aura; CGRP = calcitonin gene-related peptide.
*Groups compared with Fisher's exact test.

- **Dose?**
  - more toxicology
  - systemic effects
  - adverse events

How acceptable are challenge agents?

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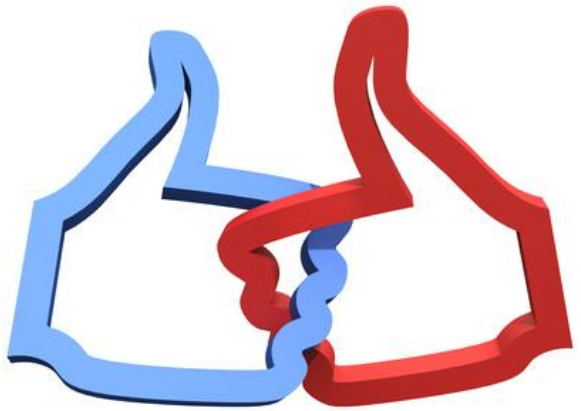

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How acceptable are challenge agents?

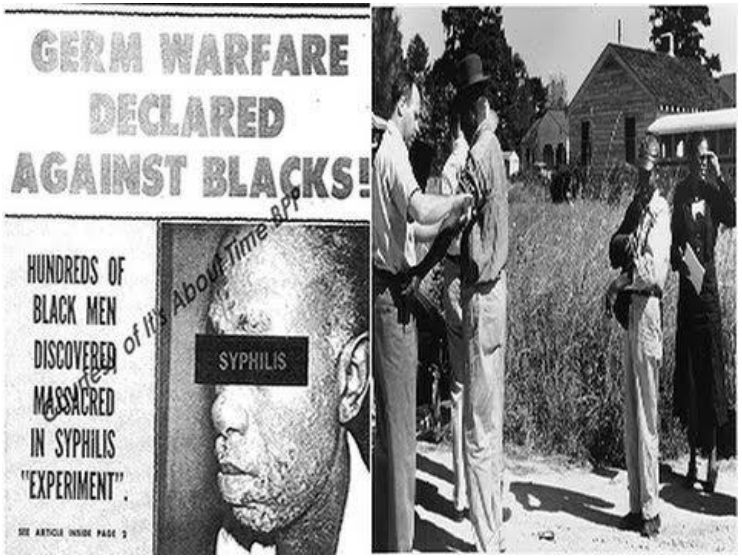
ethical considerations: deliberate infections… (1)

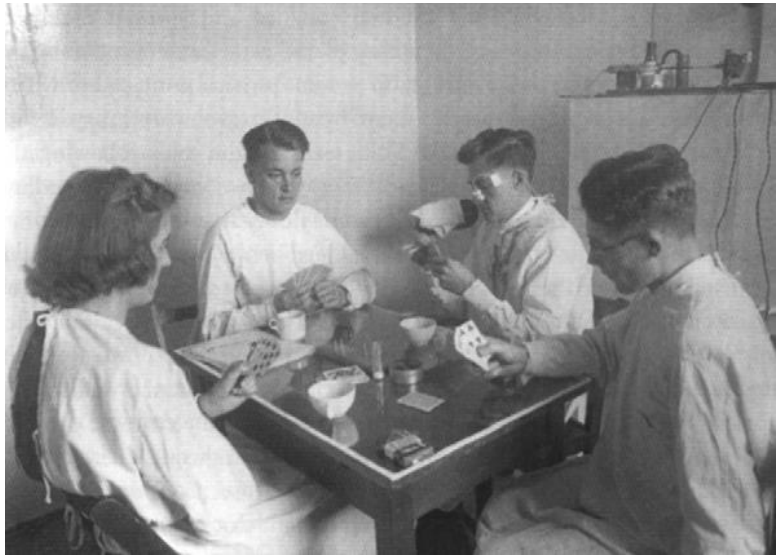
HISTORY OF MEDICINE

The Challenges of Challenge Experiments

Susan E. Lederer, Ph.D.

N Engl J Med 2014; 371: 695-697





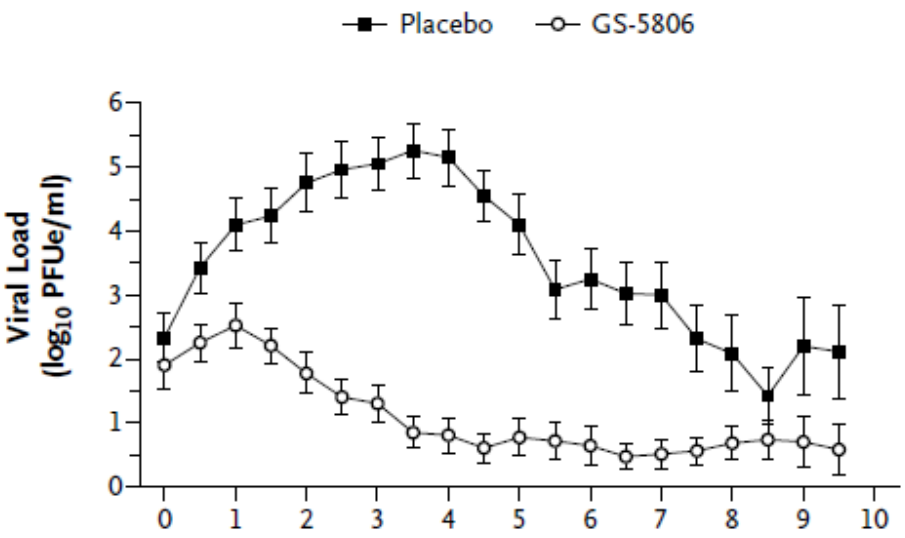
Lancet 2011; 11: 879-886

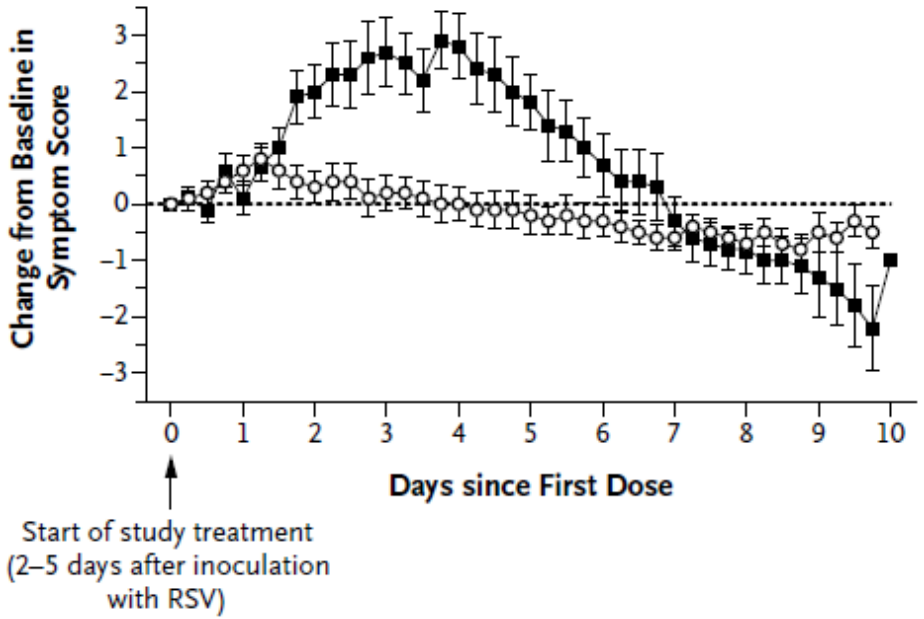
How acceptable are challenge agents?

ethical considerations: deliberate infections… (2)

ORIGINAL ARTICLE

Oral GS-5806 Activity in a Respiratory Syncytial Virus Challenge Study





N Engl J Med 2014; 371: 711-722

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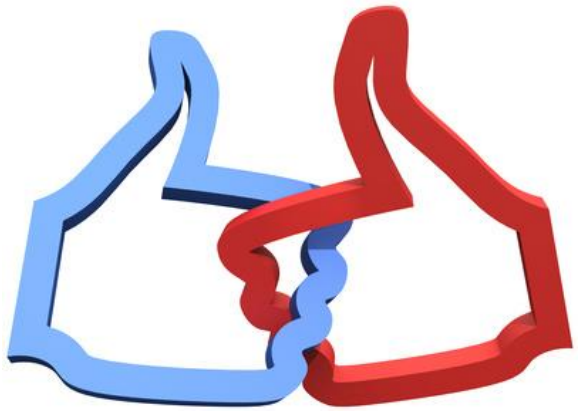

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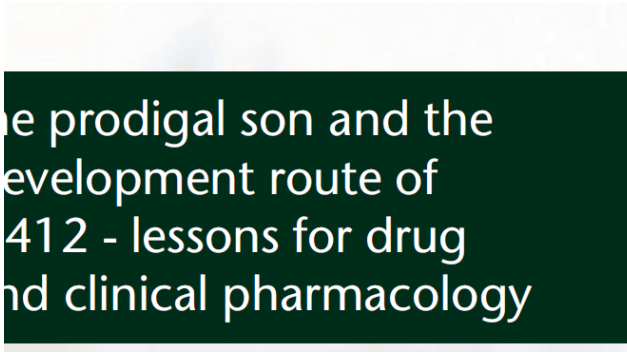
How acceptable are challenge agents?

the unexpected challenge agent…

- **TGN1412**
  - renamed TAB08
  - Russian investor
  - retested in healthy volunteers
  - starting dose 0.1% of London
  - next step: RA patients



Br J Clin Pharmacol 2015; 79: 545-547

- *"… [for scientists and regulators] to reduce their focus on regulations and increase their focus on science."*

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How acceptable are challenge agents?

the past shapes the future

- **G**
- **C**
- **P**

1493 - 1541

"… all challenge agents are poisons and there is nothing that is harmless, the dose alone decides that something is no poison."

Thank you …