The future of clinical trials and evidence generation, and their use in regulatory decision making

Setting the Scene: Problems in Drug Development

Centrale
Commissie
Mensgebonden
Onderzoek

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Joop van Gerven
chairman Central Committee on Research Involving Human Subjects

Disclaimer

This presentation represents personal views of Joop van Gerven, and not those of the CCMO.

Regulations don't provide all required evidence

- 3000 regularly applied therapies in clinical practice [1]
  - 41% proven efficacy
  - 8 % proven lack of efficacy
  - 51% insufficient evidence
- >50% treatment guidelines based evidence levels 3-4 [2]
- 61% of medical specialists [3]:
  - '¼ of treatment decisions not based on scientific evidence'

1 Clinical Evidence website 2011, how much of orthodox medicine is evidence based? 2007, Booz & Company analysis
2 https://www.demedischspecialist.nl/sites/default/files/rapport%20zorgevaluatie%20def.pdf
3 https://eenvandaag.avrotros.nl/fileadmin/editorial/docs/rapportonderzoekeenvandaagenomsevaluatieonderzoek.pdf

Providing evidence increasingly difficult: complex mechanisms and diseases

- Orphan indications
  - small numbers
  - no placebo controls
  - children (ethical limits, interaction with development)
  - misuse of orphan drug status (use expansion)
- Complex diseases
  - poorly understood diseases (psychiatry)
  - multifactorial conditions (geriatrics)
  - progressive diseases (neurology)
- 'Personalized medicine'
  - molecular targeted therapies (oncology)
  - advanced-therapy medicines (cell/gene therapies)
- Target-based indications
  - addressing common aspects of different diseases
  - crossing diagnostic boundaries (immunology)

Providing evidence increasingly difficult: limited practical significance

- placebo-controlled
  - no comparisons with available treatments
  - limited relevance for treatment decisions
- trial selection criteria
  - limited representation of clinical population
- groupwise effects
  - 'number-needed-to-treat = 7' --> *'ineffective in 6 patients'*
  - no information on sources of variability
- long-term results
  - prevention/early modification of slowly progressive disease
  - long-term safety data

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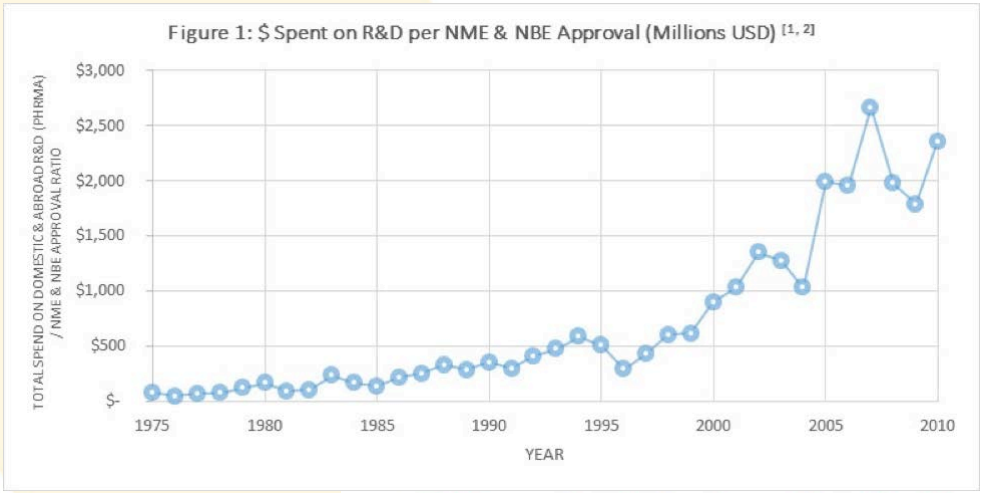
Providing evidence increasingly difficult: rising costs and diminishing productivity



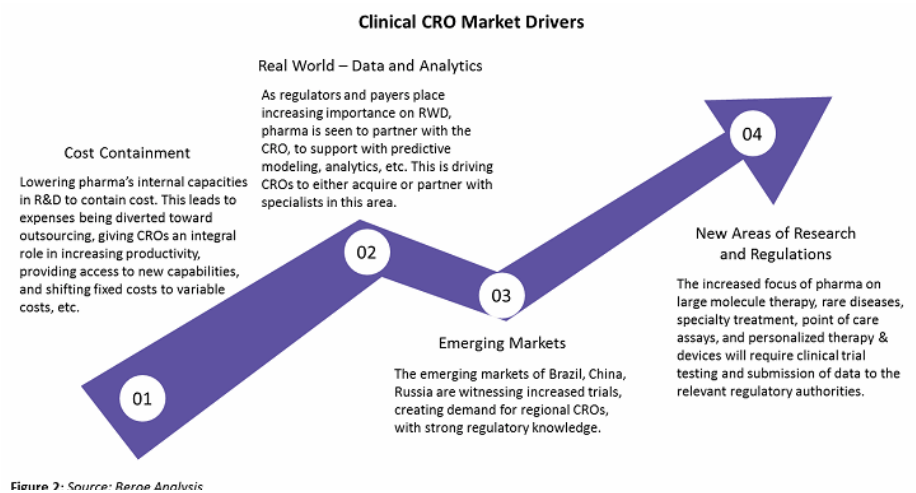
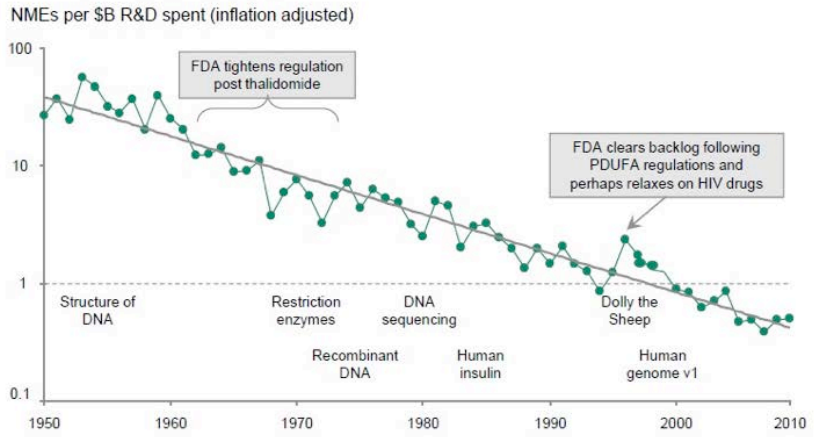


Figure 2: *Source: Beroe Analysis*

R&D productivity is on the decline

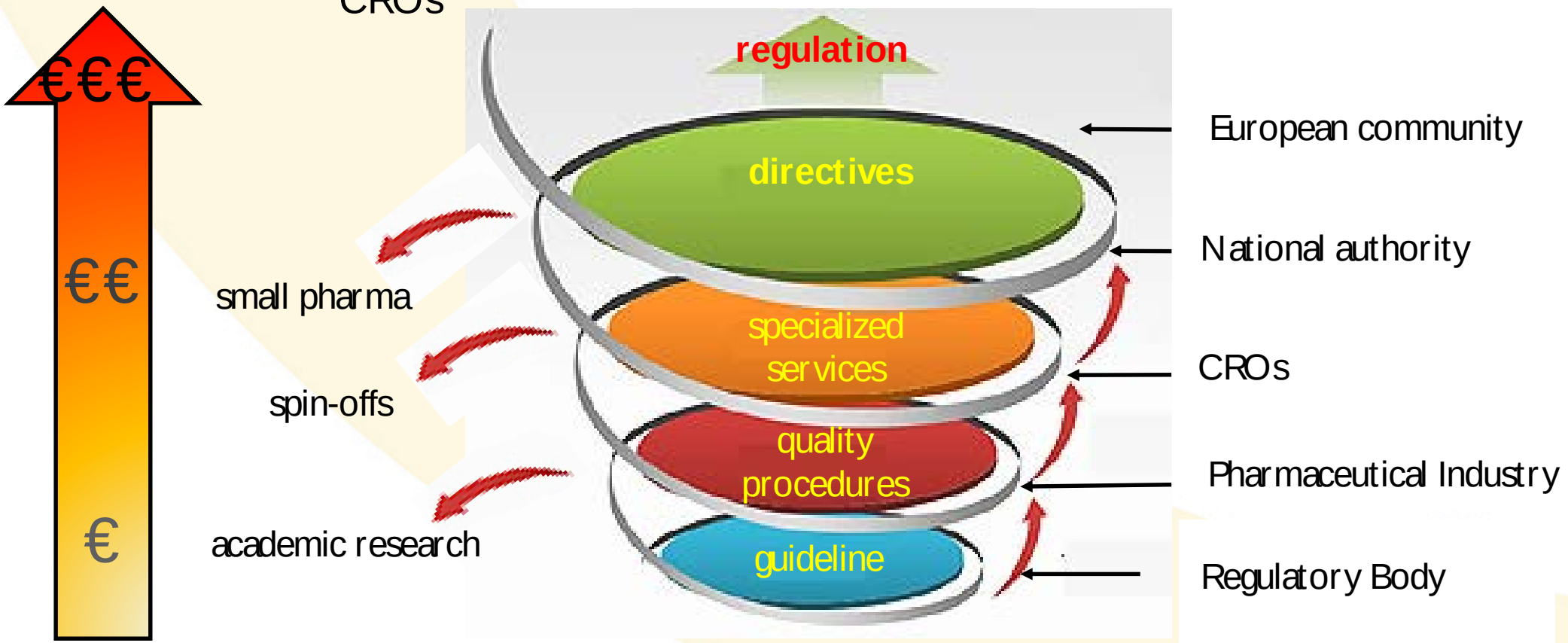


Note: R&D costs are estimated from PhRMA annual survey 2009; NMEs are the total number of small molecule and biologic approvals by the FDA
Source: Bernstein Research "The Long View – R&D Productivity" (September 30, 2010)

http://www.appliedclinicaltrialsonline.com/are-we-dismissing-business-clinical-research
https://www.clinicalleader.com/doc/surveying-the-clinical-cro-market-outsourcing-landscape-0001

Providing evidence increasingly difficult: increasingly complex regulations

- Growing numbers of guidelines and regulations
  - 2014-2021: CTR, GDPR, MDR, IVDR
- Complexity of requirements drains small innovative companies
  - academia ---> small pharma ---> large industry
  - CROs



Towards future solutions: changing drug development

- improved regulatory guidance
  - harmonisation within regulatorory chains
  - sponsor control ⟷ regulator control
  - facilitate academic drug development

- alternative clinical research structures
  - adaptive/practical trial designs
  - improved drug research infrastructure/dedicated centres

- 'trial evidence' ⟶ 'totality of evidence'
  - building chain of consistent information:

drug administration → target penetration → pharmacological interaction → pathophysiological effect → clinical improvement

  - integrated throughout development process:

preclinical → phase 1 → phase 2 → phase 3 → health care evaluation

  - co-development of biomarkers of exposure and activity
  - real-world evidence and quality of life

Towards future solutions: changing health care

- improved education and training of health care professionals
  - knowledge of molecular pathology/pathophysiology
  - knowledge of pharmacological targets
  - measurements of above (biomarkers)
  - understanding of individual sources of variability
  - target-guided treatment decisions based on above
  - 'trial-based guidelines' --> 'personalized medicine'
- learning health care systems
  - systematic evaluation of efficacy/safety as part of health care
  - based on systematic measurements of drug-target interactions in relation to pathophysiological changes
  - including real-life (ambulant) measurements
  - comparative cost-effectiveness studies in health care
- involve patients in treatment evaluation
  - treatment options include drugs in development
  - shared decision making on benefit/risk/burden
  - proportional information adapted to uncertainties
  - study design overlaps with clinical monitoring

Potential rewards

- earlier access to new treatments
- fewer late stage failures ⟶ earlier re-allocation of resources
- more practically relevant evidence
- improved academic drug development environment
- lower costs
- more effective use of regulations
- better trained health care professionals
- optimised individual treatment
- ...

Potential threats

- less control
- more/other/unknown safety risks?
- real-world restrictions:
  - NL is small
  - international pharmaceutical industries/CROs
  - complicated health care systems
  - medical/scientific/educational limitations (reforms require knowledge)
  - legal/technological limitations (ePD, GDPR, IT, big data, *etc*)
- feasibility: can drug developers and prescribers change?
- acceptability: can regulators change?


INSTEAD OF RISKING ANYTHING NEW, LET'S PLAY IT SAFE BY CONTINUING OUR SLOW DECLINE INTO OBSOLESCENCE.
TOM FISH BURNE