Where are mistakes typically made?

"Tell me where I'm going to die, so I won't go there…"

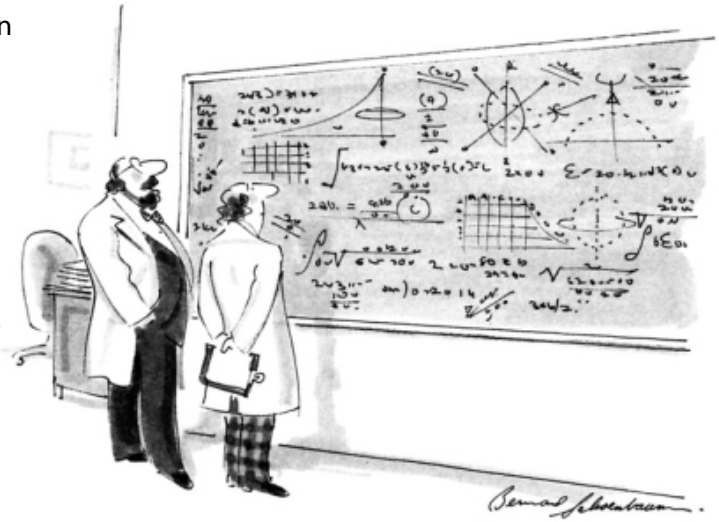
Typical mistakes

R&D/ technical

- Nonclinical: misunderstanding of science / mechanism / toxicology, CMC
- Seller may not be transparent on all information
- Clinical / observational trials: results not put in context, population not examined for representativeness, sanctity of data put aside
- Clinical / comparative trials: multiplicity error ignored, biomarkers pursued recklessly, biases not fully taken into account (e.g., ascertainment, selection, publication), missing data not treated conservatively
- Regulatory: FDA suggestions / correspondence ignored

Commercial and strategic assessment

- Errors of commission from:
  - Overly optimistic market builds
  - Overlooking competition / disruptive new entrants
  - Misevaluating sustainability of seller's aggressive marketing practices
  - Being overly driven to "do something"
- Errors of omission from:
  - Risk aversion / conservatism (e.g., with IP)
  - Consensus driven decision making
  - R&D not separated enough from BD
  - Lack of senior involvement in process till end



"Way too much information—just say that we successfully reached all endpoints."

Smoke and mirrors in data reporting and trial design

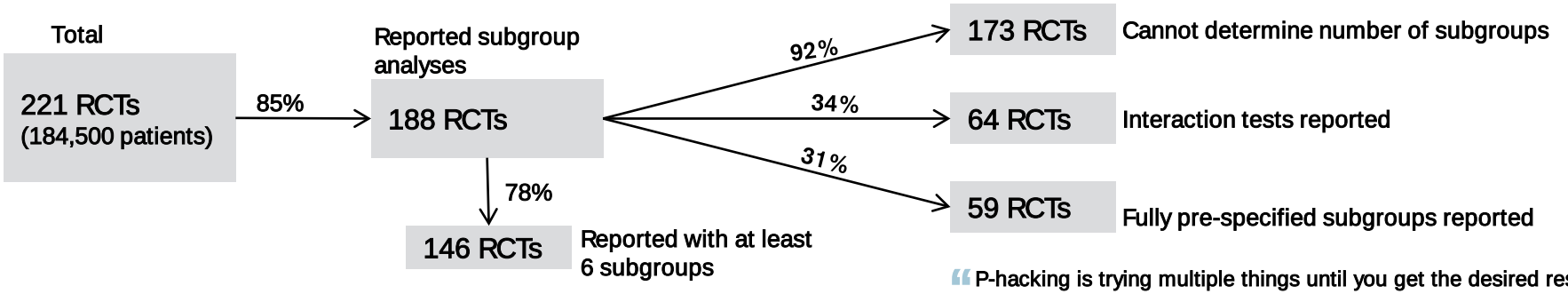
Companies are not transparent with information[1]

(n=61) Comparison of FDA letters with public announcements	% of FDA letters
Overall public statements about FDA decisions that are accurate	14%
Efficacy-related statements in CRL press releases that are accurate	16%
Safety-related statements in CRL press releases that are accurate	15%
Press releases not issued for CRL's	18%
Press releases that **do not include any statements that match the statements** included in the CRL	21%
CRLs that **include a new clinical trial requirement that reported the recommendation policy**	59%

Uncontrolled trials generally overestimate a drug's effect

	Identical chemotherapeutic agents	
	Phase 2	Phase 3
# of studies	49	43
Mean # of patients enrolled	52	363
% randomized	4%	100%
Mean RR[2] (range)	43.2 (16%–87%)	34.2 (11%–86%)

Overuse and lack of clarity of subgroup analyses[3]



"P-hacking is trying multiple things until you get the desired result [even unconsciously]."
– Uri Simonsohn, UPenn

Misunderstanding evidence leads to a porous drug filter

Symptoms

- Belief in past techniques (non-predictive, preclinical models, historical controls, invalidated biomarkers, retrospectively derived analyses, …)
- Prioritization of timelines/costs over definitive results
- The desire to avoid negative results overrides that of getting the right answer
- Easily "fooled by randomness"

Signs include

- Many publications of small, inconclusive P2 clinical trials
- Studies often not leading to additional definitive randomized controlled studies
- High P3 failure rate (for those trials that do lead to P3)

Source: Zia et al JCO 23 October 1, 2005 p. 6982-6991 and Ratain, AACR-NCI-EORTC 2007.
(1) BMJ 2015;350:h2758; doi: 10.1136/bmj.h2758, 8 April 2015.
(2) Reported response rate.
(3) Source: Zhang et al JCO 20 May, 2015 p. 1697-1702.

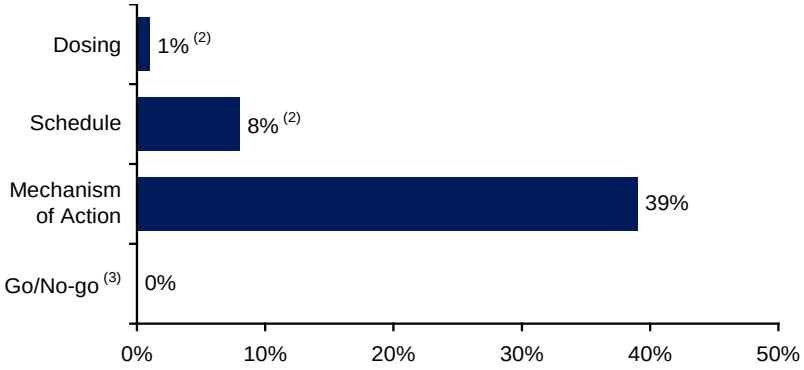
Despite being intuitively compelling, biomarkers derived from weak scientific bases or “fishing expeditions” are most often counterproductive

Limitations with using biomarkers in cancer drug development

- Biomarker selection is rarely done on a strong scientific foundation with a testable hypothesis
- "Fooled by randomness:" Multiplicity errors abound, especially if markers are assessed retrospectively.
- Use of "obvious" biomarkers have led to important cancer drugs being studied in the wrong patient populations (eg EGFR antagonists, VEGFR antagonists, Sorafenib, Estramustine, etc)
- Imprecise, non-reproducible analytics
- High cost
- Invasiveness of tests, especially tumor biopsies

To date biomarkers have rarely contributed to dose/ schedule selection or go/ no- go decisions in early clinical development

- Proportion of P1 trials whose results had primary(1) influence on clinical development parameters
- n=87 published p1 studies (Goulart et al)



Source: Clin Cancer Research 2007; 13(22) pp 6545–6546, 6719–6725.

(1) "Characteristic that is objectively measured and evaluated as on indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention."

(2) NB drug dosing increased in P3, so biomarker may have paradoxically impeded development.

(3) By inference.

There Are Several Elements to Drug Value

Elements of Drug Value	How Quantified	Beneficiaries	Timing of Benefit	Timing of Payment (to manufacturer)?
Outcome at episode of care	QALYs, HTAs at Time 0	Patients receiving drug	Today	Today
Perpetuity value	QALYs, HTAs over itime indefinitely	Patients receiving drug	Post patent expiration	?
Option value	Various methods to assess novelty and "upside" eg risk adjust NPV, real options pricing	Society and patients receiving drug (for future indications)	When there is evidence of efficacy	?
Intangible value/ hope	willingness to pay (WTP) analyses that measure value via trade offs	Society especially those at risk for certain disorders or with family members with said disorders	Today and forever	?
Innovation	willingness to pay (WTP) analyses	Society if productive innovation	Today and forever	?