Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Department of Medicine

Basel, 28 June 2018

Swiss TPH Summer Symposium

Approaches, Success Stories and Challenges
The Academia Perspective

Agenda

Not looking into academic trial – but an academic look at trials…

- Does the PDP model deliver?
- Does the Pharma model deliver?
- Thoughts about trial efficiency
- Thoughts about the bigger picture
- Conclusions

Starting point
Perception

- Maximum public health impact in PDP vs maximum profit in industry
- Very lean R&D vs very high expenditures
- Key contributions and impact vs mainstream

➢ Some reflection about approaches and parameters might be useful

Starting point
A few facts of life

- **Moore's law** by Gordon Moore, founder of Intel

  Observation that the number of transistors in a dense integrated circuit doubles about every two years
- **Eroom's Law** (Moore's Law backwards) by Jack Scannell

  Exponential decline in R&D efficiency in the drug industry between 1950 and 2010

- **Murphy's law**

  Anything that can go wrong will go wrong
- **Burri's law for clinical research**

  Even if nothing can go wrong will go wrong

PDP working model

Example MMV

Poverty related and neglected diseases

The PDP model delivers

- 1996 - IAVI International AIDS Vaccine Initiative launched
  - First biomedical product development public-private partnership
- 7 out of the 18 drug approvals for new chemical entities (NCEs) targeting neglected diseases since 1989 result of the work of PDPs
  - PDPs account for 39% of drug development for neglected diseases
    - 22% private companies
    - 17% from philanthropic endeavors
    - Smaller percentages as a result of military, priority review vouchers, and IP transfer (including malaria and TB)

➢ "PDPs are serious" F. Bompart (Sanofi now DNDi), Nature 2016

Source: PhD thesis Julia Tuttle, UN Durham 2016; Rahman 2015

Poverty related and neglected diseases

PDPs work highly efficiently

- 2017 - 538 product candidates for 35 neglected diseases identified
  - Portfolio-To-Impact (P2I) model used

➢ Estimated resulting product launches till 2030
  - 43 products for poverty related neglected diseases
  - 85 for TB, malaria, HIV

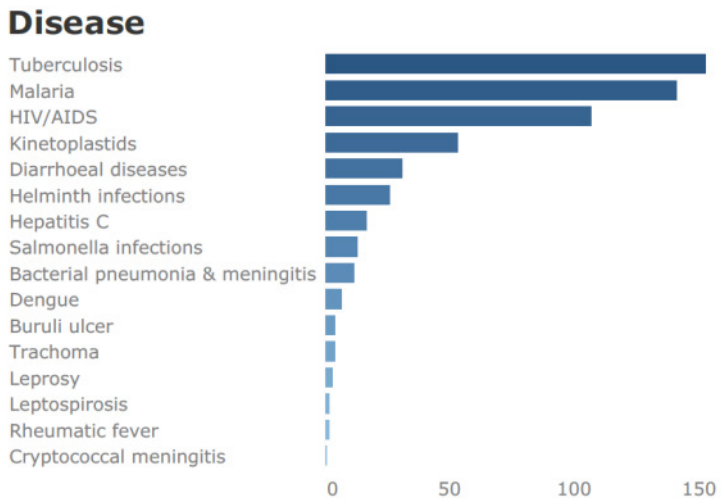
➢ Estimated expenditure for development: $16.3 billion (range $13.4-19.8)

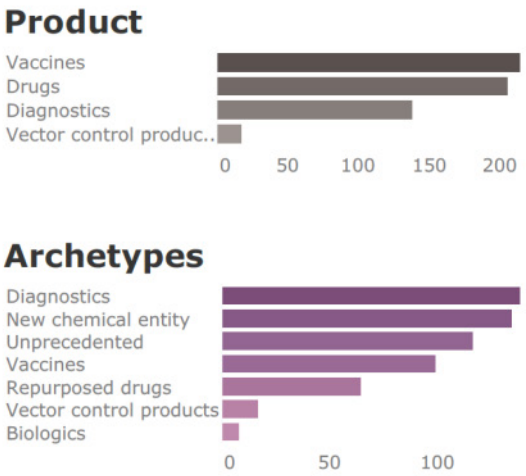
  ➢ Average about 130 Mio per new product – match to published figures
    - Excludes CMC, scale up, manufacturing

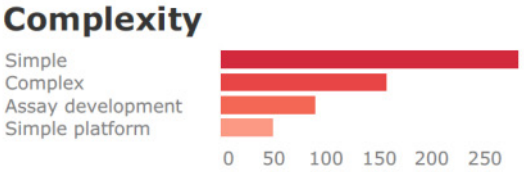
Sources: R. Young, Gates Open Research 2018, Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model
A. Maxmen 2016, Nature, Big Pharma's cost cutting challenger

Poverty related and neglected diseases

Academia, PDP and industry impact







Source: G-Finder 2017, Neglected Tropical Diseases R&D product pipeline

Success in PDP models ?

Caveat - Sustainable Development Goals

- Sustainable Development Goals (SDGs) state
  - By 2030, “end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases”
  - End preventable deaths of newborns and children under 5 years of age
  - Reduce global maternal mortality ratio to under 70 per 100,000 live births

➢ Result of recent studies modelling impact of scaling up health tools and strengthening health systems
  - Highly unlikely these targets will be achieved today’s health technologies alone
  - Will also require breakthrough innovations, such as high efficacy preventive vaccines for HIV, malaria, Hep C and tuberculosis
    - ➢ Estimated costs for these products are close to 1 Bio per product !

Sources: R. Young, Gates Open Research 2018, Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model

The Pharma model

Costs of development

- Average costs per new drug: US $2’558 million
  - Average of 106 drugs entering clinical research between 1995 - 2007
  - Out-of-pocket cost of US$1’395 million
  - Capital costs US$1’163 million

➢ 145% increased since 2003 = annual growth rate of 8.5%

- Costs for Phase I: 30 Mio, Phase II: 65 Mio; Phase III: 253 Mio
- Costs for Phase III studies increased over proportionally
  - Ratio between Phase III and II costs was 5.7 in 2003, 10.1 in 2016
  - Ratio between Phase II and I costs was 3.7 in 2003, 4.4 in 2016
  - Phase I costs increased by 28% between 2003 and 2016

Source: Di Masi et al. Journal of Health Economics, 2016 / Di Masi et al. Journal of Health Economics, 2003

The Pharma model

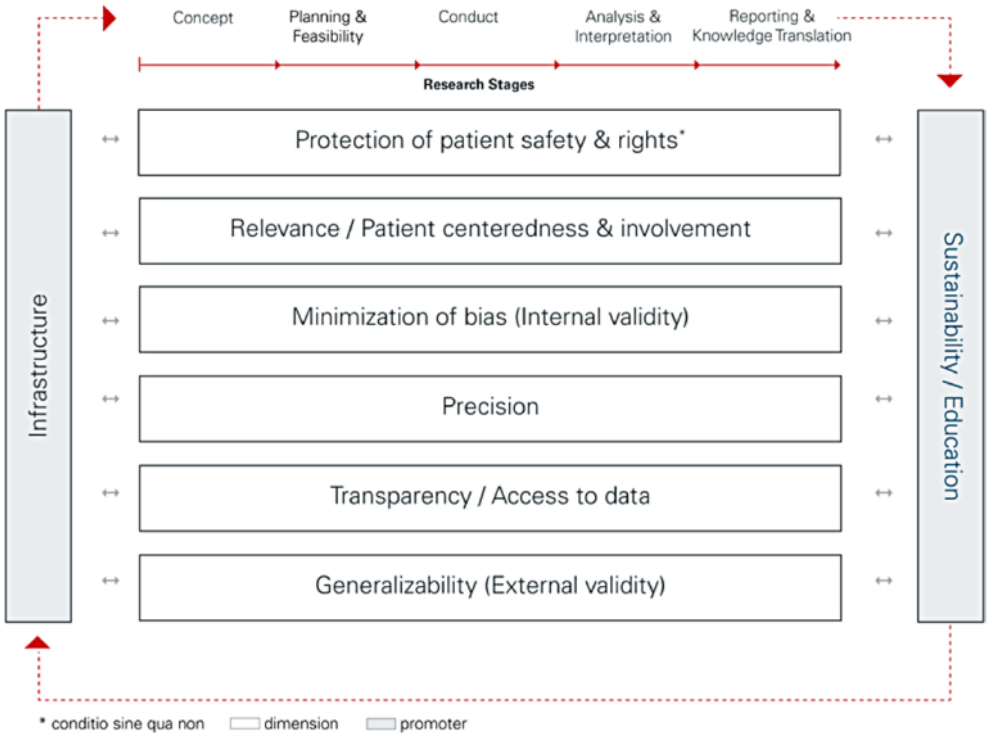
Reasons stated for increase

- Main reasons indicated
  - Higher failure rates for drugs tested in human subjects
    - ➢ 2003: 1/5 product successful; 2016: 1/8
    - Greater focus on targeting chronic and degenerative diseases
      - Alzheimer modifying approaches had a 99.8% failure rate so far
  - Increased clinical trial complexity
  - Larger clinical trial sizes
    - Less well defined endpoints
    - Regulatory requirements (e.g. diabetes)
- But aren't there others….
  - Legal requirements
  - "Quality" requirements
  - Not so creative scientific approaches – study design, event reporting

Source: Di Masi et al. Journal of Health Economics, 2016 / Di Masi et al. Journal of Health Economics, 2003
L.Cummings, Alzheimer Re Ther 2014, Azheimer's disease drug-development pipeline: few candidates, frequent failures

Reflections on quality

Definition of clinical trial quality

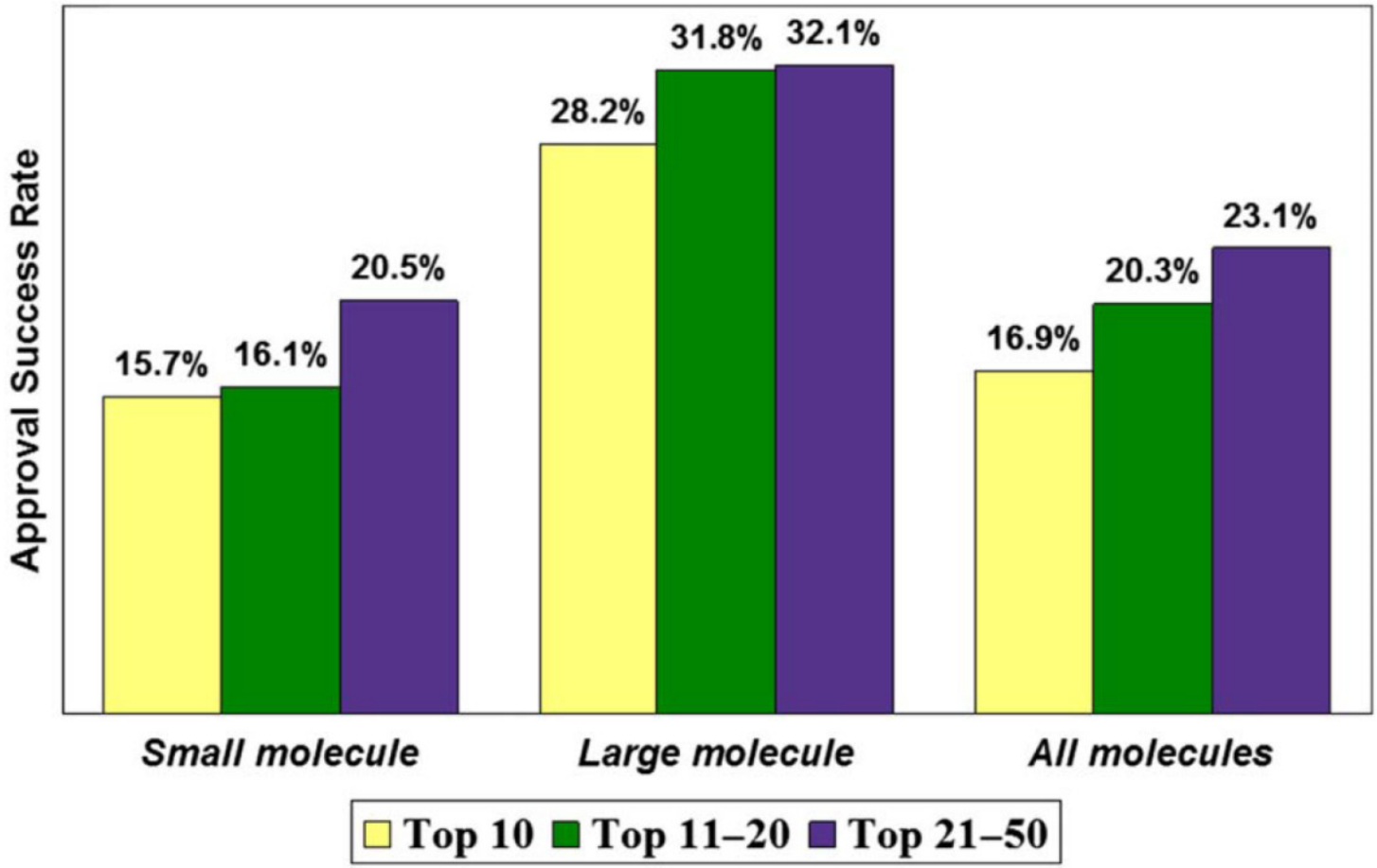


Number of Interviewees stated the theme	Themes	Quality relevant aspects
6	Quality system	- quality management system - looking at all aspects - set up a system for all aspects - cover many aspects and not only one - quality can be assessed by many different things - fulfilment of many aspects needed - the aspects are interplaying - a set of factors enabling collection of data - many aspects through the different clinical trial steps - steps taken to ensure the smooth running of a clinical trial
	Data integrity	- integrity of clinical trial data - integrity of clinical trial data reflects quality - collect data that will lead to correct conclusion - reliability of data - credibility of data that are close to reality/ truth - quality equals data integrity plus ethics
	Rigorous adherence to predefined standards/ methodology	- presence on site/ oversight/ supervision - strict/ disciplined following of rules - setting priorities - sticking to the plan even in stressful situations - strictly following the methodology step by step - rigorous execution - compliance with the requirements - quality can depend on the expertise of monitors - alignment of objectives - awareness of quality requirements
5	Soundness of research	- a good quality trial leads to valuable results - sound scientific premise - minimization of bias / confounding - sound design (well-thought & planned) - sound depends on the methodology applied - sound conduct - ability to get accurate/ valid information for a specific study - reaching the study objectives
3	Ethics	- light system not heavy system, targeted to the main risks - the benefit should be rather early than rather late - quality equals data integrity plus ethics
2	Collaboration	- desired by the local investigators - partnerships - motivation - good team
	Documentation	- having a trial master file improves clinical trial quality - missing enrolment logs is low quality
	Context dependent	- goes beyond SOPs (not just one aspect, not just SOPs) - having clever approaches (*e.g.* for patient recruitment, data oversight/monitoring) - the aspects (or the choice of aspects) defining the quality may vary
	Participant safety	- protecting the safety of participants in a clinical trial - applying all necessary safety measures - having a safety awareness
	Health improvement	- life improvement of vulnerable population - target population benefits from the clinical trial
1	Meeting everyone's expectations	- aspects may be the expectations by all the parties involved (*e.g.* sponsors, (local) investigators, CRO)
	Relevance of research question	- having an important research question

Source: C. Fuchs, MSc Thesis Quality in clinical trials – A resource-limited settings perspective (unpublished data)
von Niederhäusern 2018, PLOS Medicine, A comprehensive framework for INQUIRE

Reflections on output

The right approaches



Source: Di Masi et al. 2014, American Journal of Therapeutics, Pharmaceutical R&D Performance by Firm Size

Reflections on efficiency

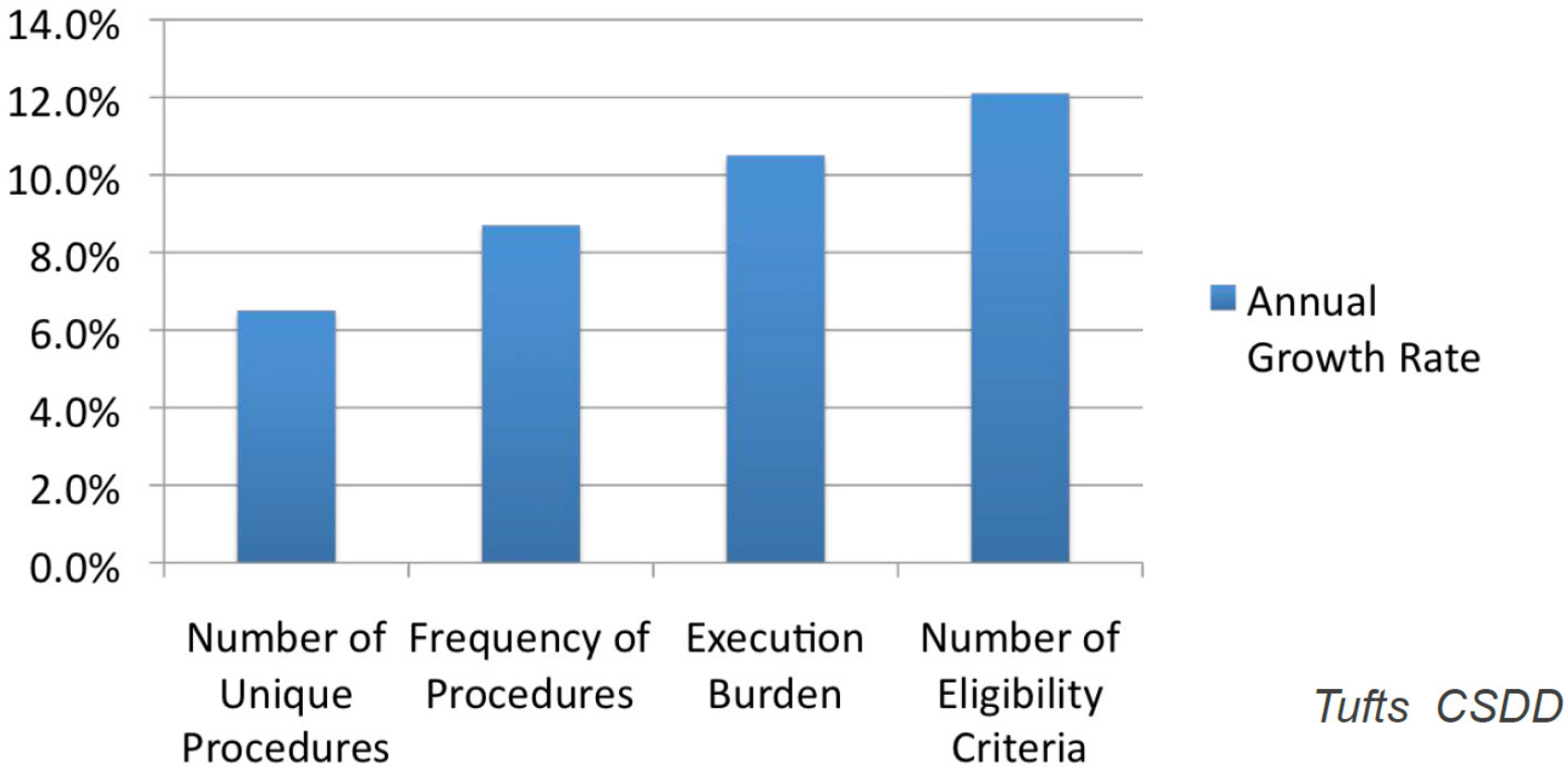
Factors delaying clinical trials

Ethics committee review and approval	51%
Patient recruitment and enrolment	33%
Legal review	26%
Contract and budget negotiation and approval	22%
Protocol design and refinement	21%

Source: DIA risk management training, session 14

Reflections on efficiency

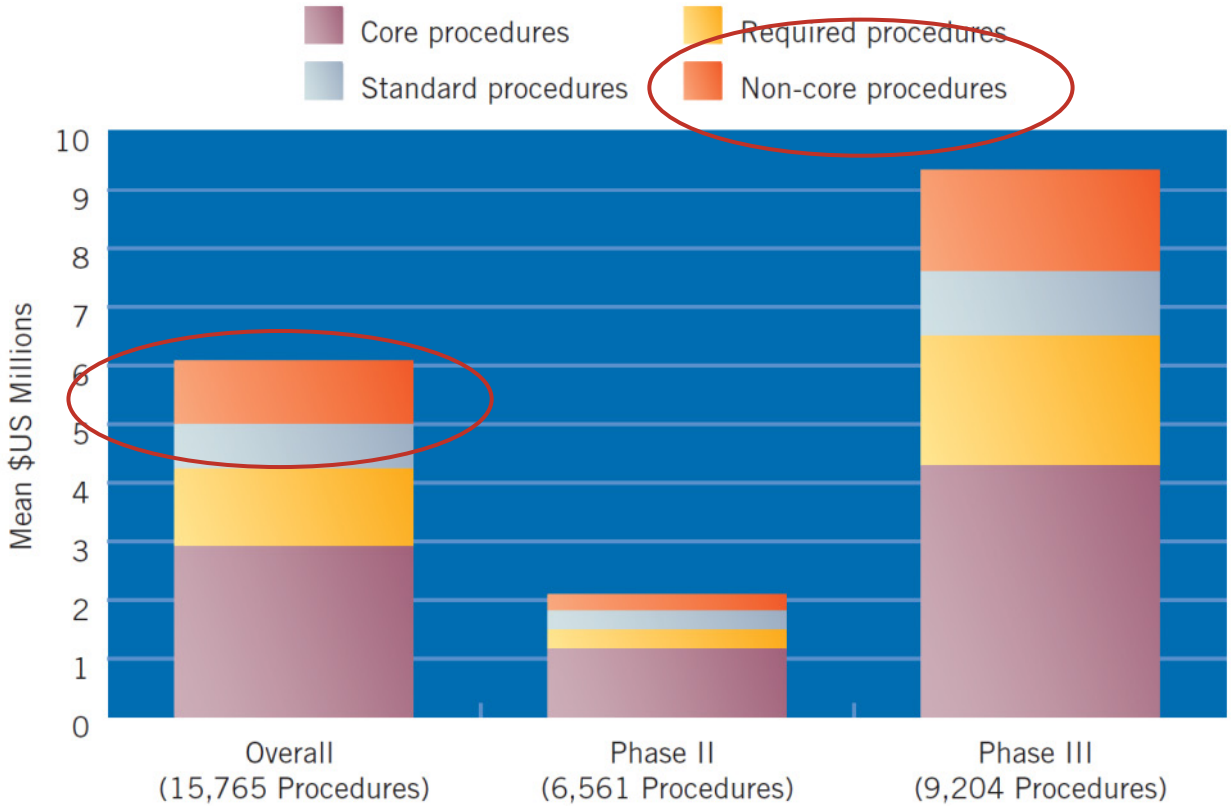
Thoughts on trial design



Source: Source: Getz K. Regulatory Affairs Journal Pharma. 2008:315–6 – adapted by DIA (risk management training, session14)

Reflections on efficiency

Doing the right thing



18% of a study budget spent on non-core procedures
Eliminating could save up to $6 billion per year

Source: Tufts Center Outlook 2013

16

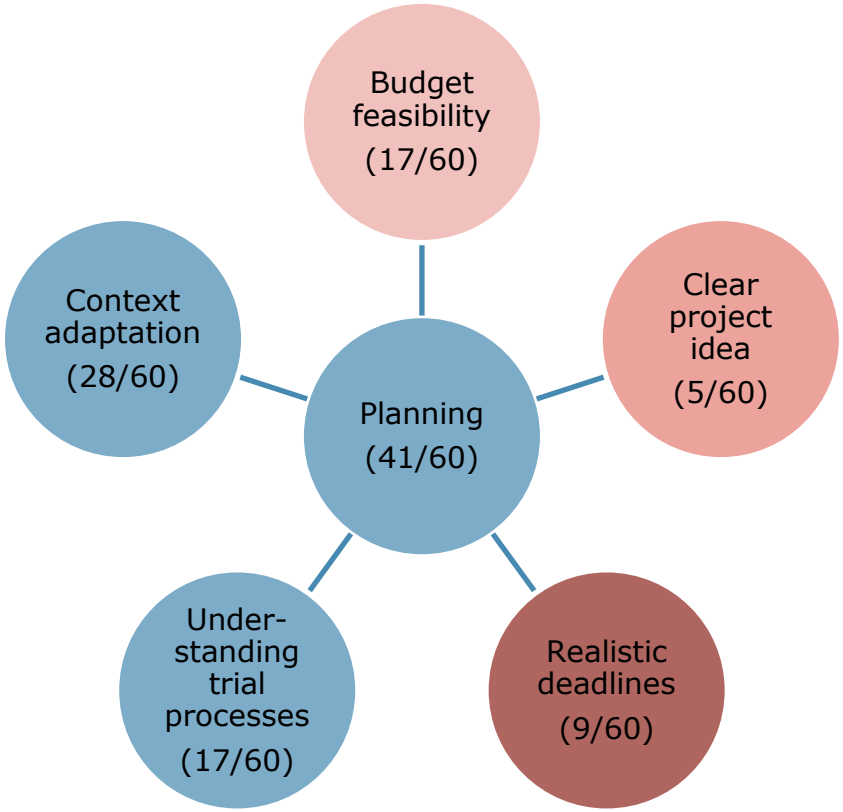
Reflections on efficiency

Checking the right things

- Monitoring
  - Risk based monitoring encouraged by authorities – acceptance?
  - Many companies still go with 100% SDV….
    - This mainly helps the CRO industry
  - Remote monitoring
- Alternative monitoring – do the right things
  - Staff training is considered more cost-effective than on-site monitoring
    - Why not invest in continued training instead and monitor knowledge
  - Good communication is key for a trial
    - Why not invest in having satisfaction of communication lines assessed
  - Smart planning and approaches would save major amounts of money
    - Only 21% of trials ongoing in 2014 used adaptive approaches
    - Why not invest in “monitoring” the trial approach – cross-check
  - Prevention instead of monitoring SAEs

Reflections on efficiency

Improvement of protocol suitability (Sub-Saharan Africa)



Source: PhD Thesis N. Vischer, Efficiency and quality in conducting clinical trials in Sub-Saharan Africa 2016

Reflections on efficiency

Thoughts on trial design – amendments

- Amendments cause delays and impact trial costs

  - 3'410 protocols analyzed
  - Nearly 60% had at least one substantial amendment
    - Phase II mean of 2.7 amendments
    - Phase III mean of 3.5 amendments
  - Average of 7 changes per amendment
  - 40% of amendments occurred before first volunteer, first dose

  - 34% of protocol changes were avoidable
    - Design flaws, inconsistencies, protocol errors
  - Median direct cost to implement a substantial amendment
    - $ 450'000 (without internal FTEs)
    - Mainly increased site and third party costs

Source: Getz K., Applied Clinical Trials 2016, Protocol Amendments: a Costly Solution,

The bigger picture
The right attitude

- "It is a great mistake to think that the bare scientific idea is the required invention, so that it has only to be picked up and used. An intense period of imaginative design lies between" A. Whitehead 1925
  - Translational research
    - Requires to incorporate cutting edge science
    - Requires the collaboration of multiple disciplines
    - Relies on ingenuity
    - Is different for each challenge
    - ➢ This makes it inherently messy and difficult to be reduced to optimized processes

➢ True breakthroughs are driven by vision and passion, not risk assessment and net-present value calculations

- A fast follower attitude will not maintain the vitality of industry
- Target based research will yield some output, but likely not breakthroughs

Source: Munos, Nature 2010, Can open-source drug R& D repower pharmaceutical innovation ?

The bigger picture

The right approaches

	✓ Managing for operational excellence	✗ Managing for breakthrough innovation
Goal	Defend and grow current business	Replace current business
Focus	Current markets and customers	New technologies and products
Culture	Efficiency, discipline, order Improve, optimize	Intuition, ambiguity, opportunity Disrupt
Organization	Hierarchical, differentiated, complex	Light, flexible, fluid
Processes	Numerous, exacting, formal Focused on planning and execution	Fewer, fuzzy, informal, adaptive Driven by intuition
Thinking	Aligned	Orthogonal
Decision making	Analytical, rule-based, cautious	Intuitive, vision-driven, bold
Working style	Sticks to job description	Crosses boundaries
Personality	Conforms, fits in	Sticks out, frequent outliers
Environment	Risk-averse, change-wary	Risk-taking, change-friendly

Source: B Munos, Nature 2010, Can open-source drug R& D repower pharmaceutical innovation ?

The bigger picture

The right collaborations

Percentage of collaborators with experience of issues with industry

Source: P. Vallance 2010, Nature, The Future Is Much Closer Collaboration Between the Pharmaceutical Industry and Academic Medical Centers

The bigger picture

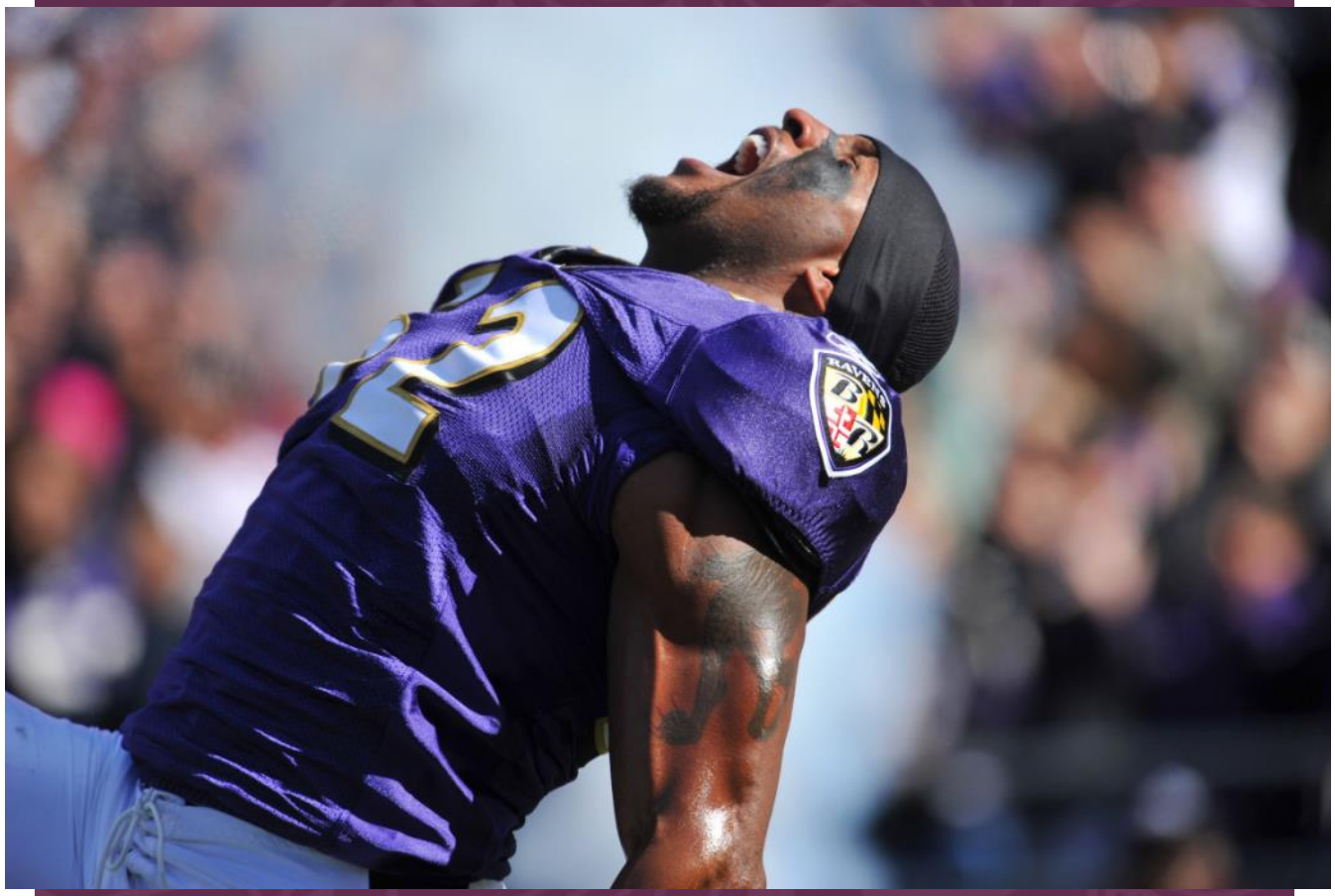
Human factor

- Everybody should do what they can do best
- Genuine interest
- Motivation
  - Motivation of individuals is a game changer

- Team size
  - Not the largest, but the best
  - Costs of coordination
  - Team stability
  - Not vendors but partners (with responsibility)
  - Knowing and trusting partners

The bigger picture

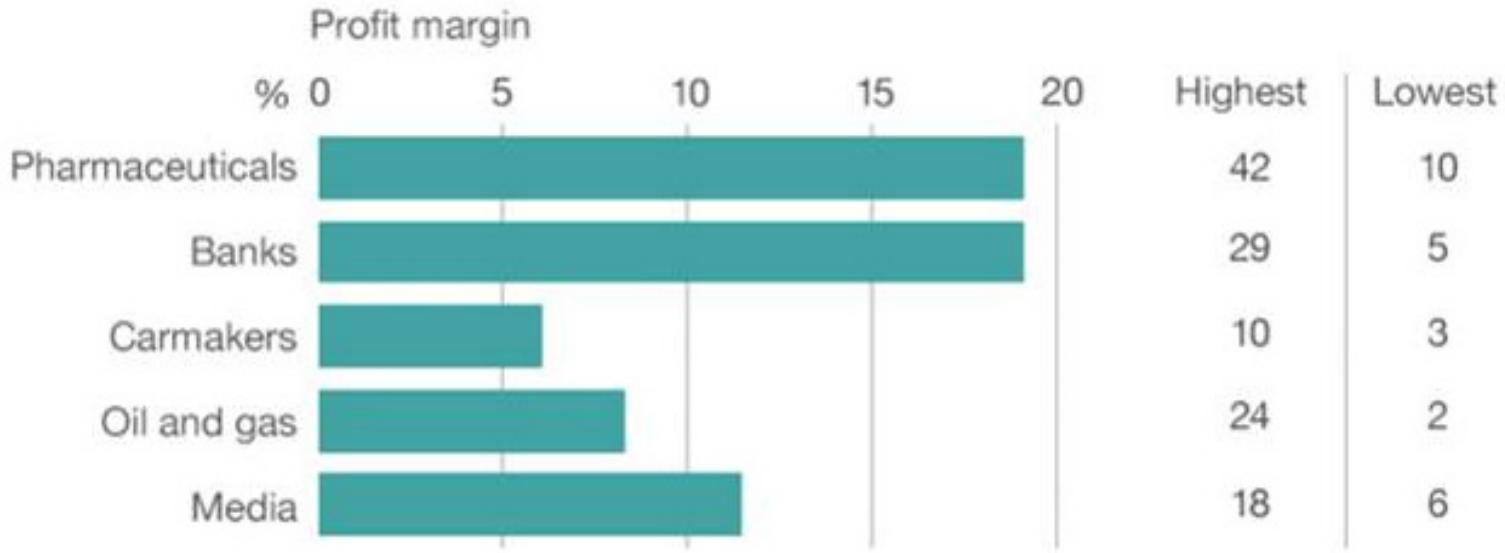
Key factor - Enthusiasm



The bigger picture

Cost of goods….

- R&D costs have direct and indirect impact on costs of a product
  - Supportive actions
    - Priority approaches for true innovation with impact on Public Health
    - Patent duration – shorter….. or actually longer?
  - True cost containment



Source: BBC News 6 November 2014 / Forbes

Conclusions

Doing things right

- Small steps - “create a better mechanism”
  - Leaner processes
  - Quality by design
  - Quality control and assurance truly according to identified risks

Conclusions

Doing things right

- Medium steps - “create a better environment”
  - Collaboration and exchange between companies, academia
  - Consortium approaches – everybody does what they can do best
    - Partially started
  - Regulatory framework fully integrating and accepting risk based approaches

Conclusions

Doing things right

- Large steps - “create a better world”
  - Consideration of human factor
  - Provide access to interventions in an equitable not equal way
  - Accept life is dangerous to life
  - Normalize profit margins

Final remark

Success of the PDP model – and beyond

- We can contribute to the accomplishment of the goal – the more efficient funds are used, the more products may come to market
- We may learn from the low income country processes to make drug development leaner and more efficient

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