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DEDICATED DRUG DEVELOPMENT XPERTS

Leveraging Clinical Trials and Conditional Approvals for Early Market Entry

Dutch Life Science Conference, Dec. 12, 2024

Ronald van der Geest PhD,
Partner at 3D-PharmXchange

Our core expertise

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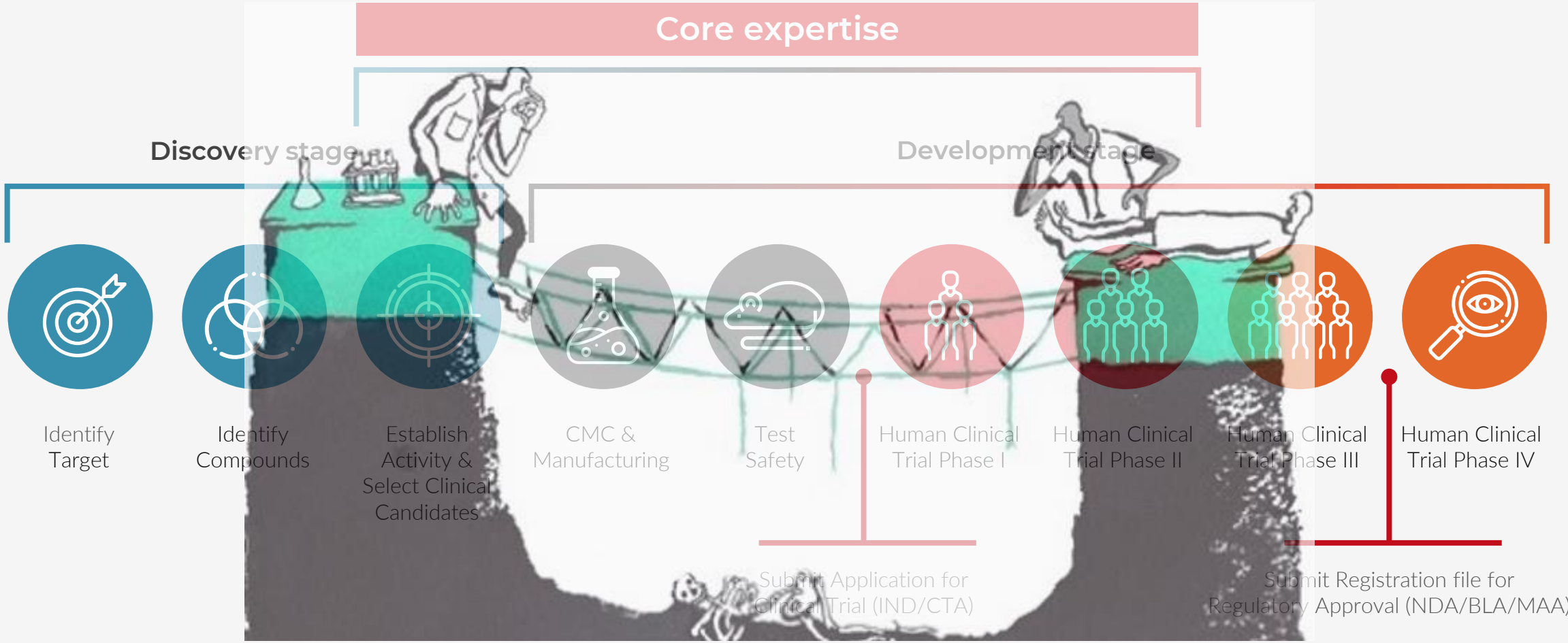

"The Valley of Death in early-stage drug development"

Are we “Lost in translation”??

Quoted from BioBooster

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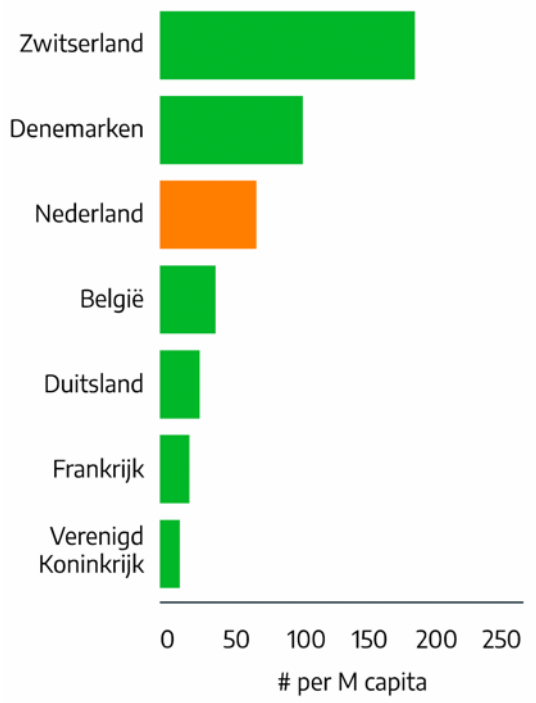
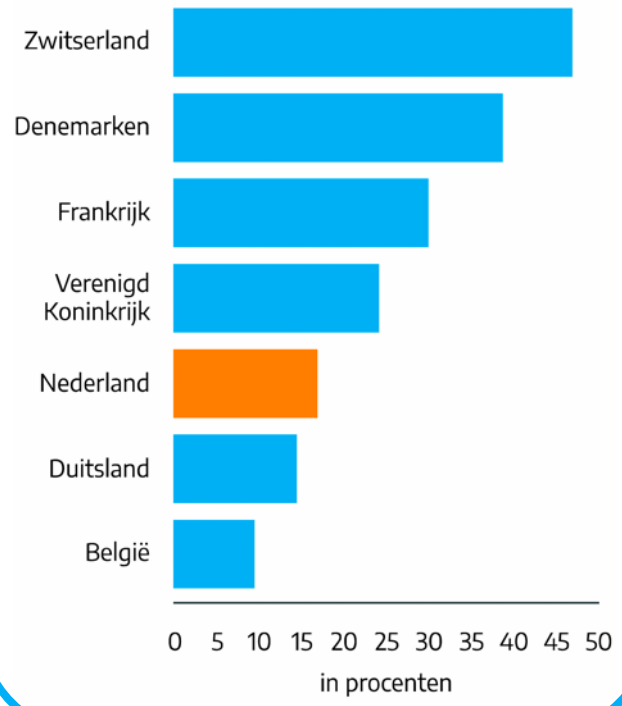
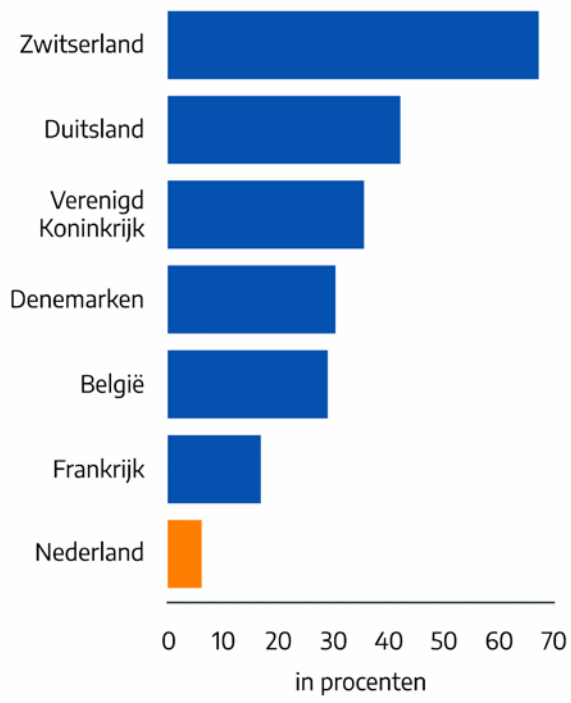
Life Sciences Octrooiaanvragen 2019[1]



Groei life sciences R&D bedrijven 2015-2019[2]



Groei life sciences R&D producten in ontwikkeling 2015-2019[3]



2021 R&D investments of the pharma industry in Europe

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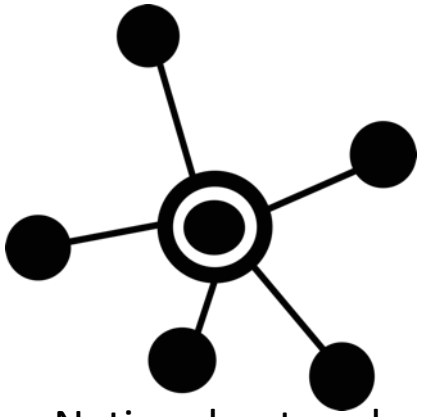
PHARMACEUTICAL INDUSTRY RESEARCH AND DEVELOPMENT IN EUROPE

EFPIA 2021	€ million		€ million
Austria	283	Latvia	n.a
Belgium	5,196	Lithuania	n.a
Bulgaria	95	Malta	n.a
Croatia	40	Netherlands	900
Cyprus	85	Norway	126
Czech Rep.	75	Poland	321
Denmark	1,114	Portugal	121
Estonia	n.a	Romania	72
Finland	234	Russia	706
France	4,451	Slovakia	35
Germany	8,540	Slovenia	230
Greece	95	Spain	1,267
Hungary	298	Sweden	1,104
Iceland	n.a	Switzerland	8,232
Ireland	305	Turkey	71
Italy	1,680	U.K.	6,857
TOTAL			42,533

The Biotech Booster Program

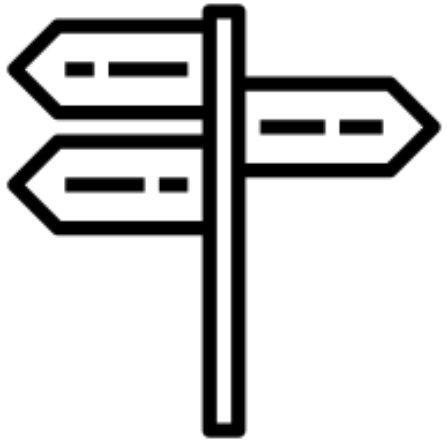
National team

Ecosystem/ Community



National network

Financing L1&2



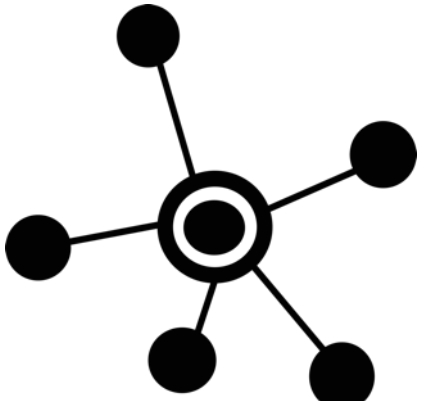
Guidance/ expertise

Training

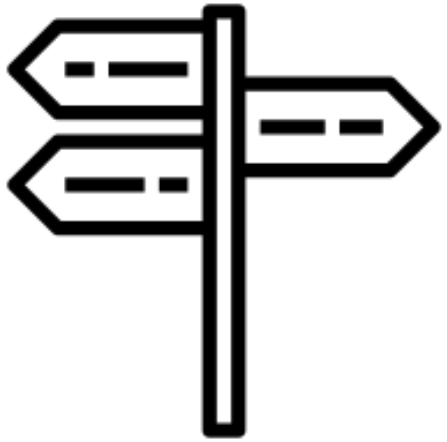
The Biotech Booster Program

National team

Ecosystem/ Community



National network



Guidance/ expertise

Financing L1&2

Training

Did we solve everything by putting this in place???

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“Late-stage Troll Wall”

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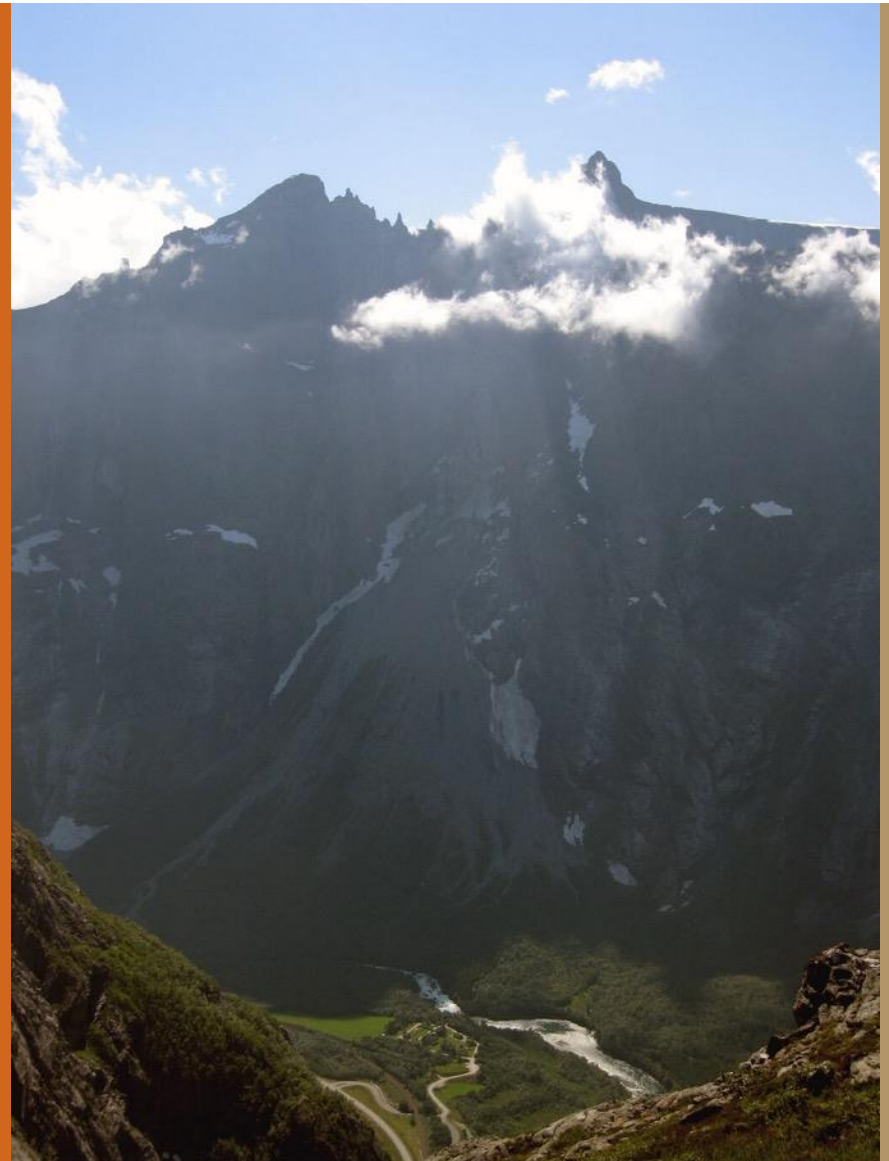

“… formed into a broken rock wall of huge corners, concave roofs, and crack systems, topped with a series of spires and pinnacles on the summit rim. The rock is generally loose, and rockfall is the norm …”

Wikipedia 2024

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TREEWAY®

Nota de prensa

Ferrer reports top-line results from Phase III ADORE study in ALS

Ferrer reports that Phase III ADORE (EudraCT 2020-003376-40 / NCT05178810) clinical trial of oral edaravone formulation (FAB122) in amyotrophic lateral sclerosis (ALS) patients did not meet primary or key secondary endpoints.

ADORE
ALS DECELARATION STUDY WITH ORAL EDARAVONE

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ADORE
ALS DECELARATION STUDY WITH ORAL EDARAVONE

Can we be smart about improving the likelihood of success?

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Strategies to improve your likelihood of success

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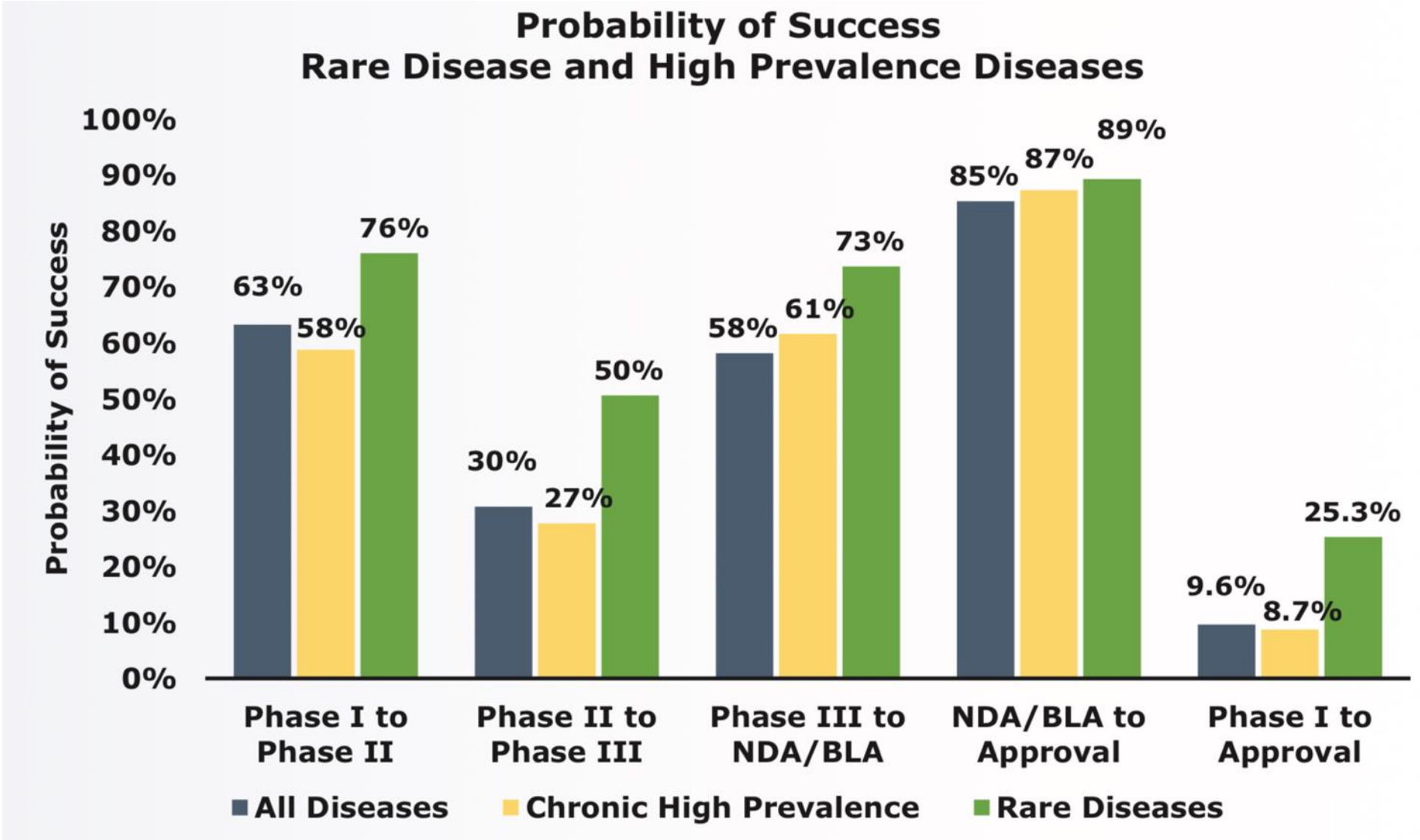

Strategies to improve your likelihood of success (2)

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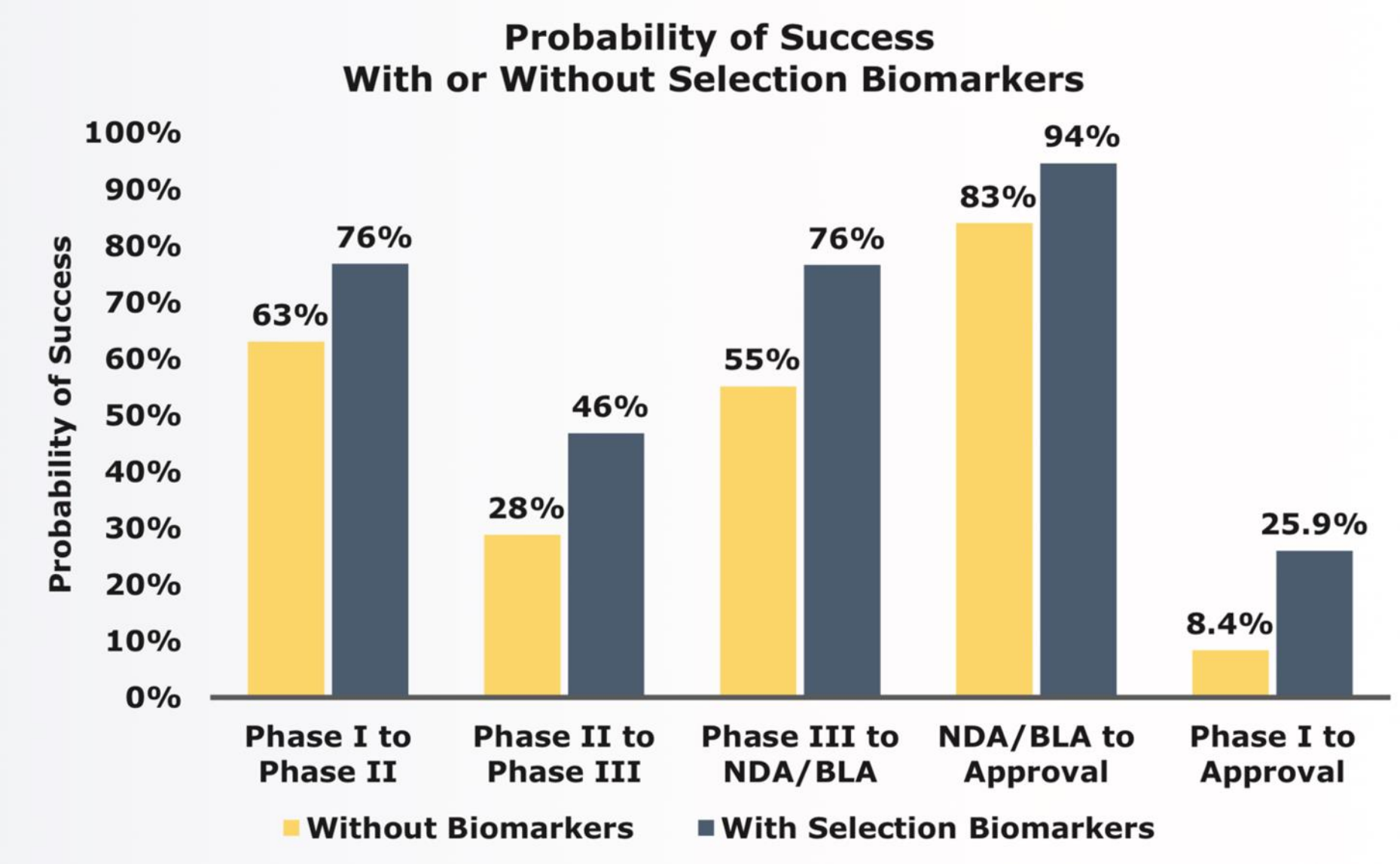

Strategies to improve your likelihood of success (3)

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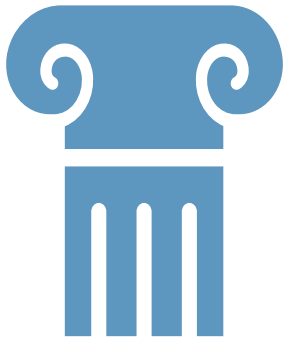
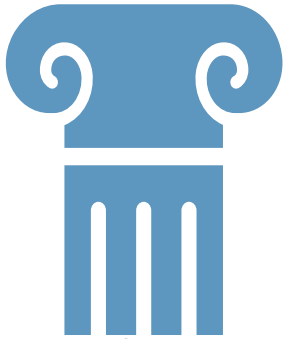
For oral small molecule drugs

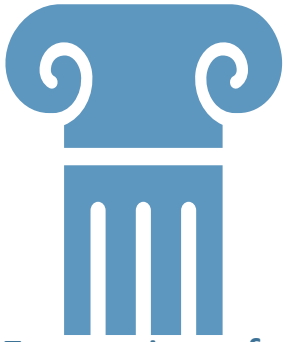
'Three Pillars of Survival'



Exposure at Target Site



Binding to Target



Expression of Pharmacology

Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Paul Morgan[1], **Piet H. Van Der Graaf**[1,2], piet.van.der.graaf@pfizer.com, John Arrowsmith[3], Doug E. Feltner[4], Kira S. Drummond[5], Craig D. Wegner[6] and Steve D.A. Street[7]

Strategies to shorten your development pathway

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Define your Target Product Profile as early as possible	target population definition & selection definition of endpoints
Smart study design	adaptive trials combined trials
Smart program design	trial expansion early HA validation

Strategies to shorten your development pathway: **case 1**

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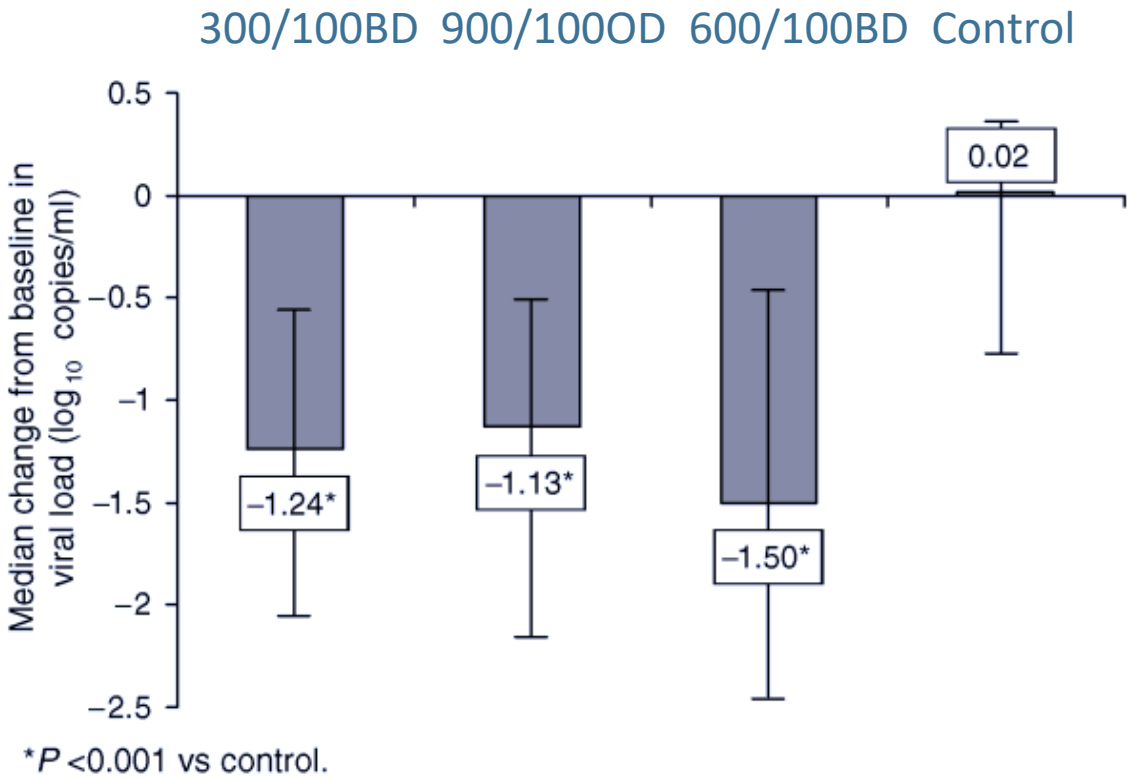

TMC114, a potent next-generation protease inhibitor: characterization of antiviral activity in multiple protease inhibitor-experienced patients participating in a Phase IIa study

S De Meyer, M Peeters, C Jordens, P McKenna, R van der Geest, R Pauwels and M-P de Bethune. Tibotec, Mechelen, Belgium and Virco, Mechelen, Belgium
12th International HIV Drug Resistance Workshop 2003

- Condition 1:
  "your data must look really great"
- Tibotec's TMC114/ritonavir substitution for protease inhibitors in a non-suppressive antiretroviral regimen: **a 14-day Ph2A trial**
- Prezista® got **accelerated approval** on phase 2B data for treatment-resistant HIV patients

Strategies to shorten your development pathway

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Regulatory Frameworks Supporting Conditional Approvals based on promising clinical data for unmet medical need indications

- **FDA's Accelerated Approval Pathway**
  - For **unmet medical needs** in serious conditions based on surrogate or intermediate clinical endpoints
- **EMA's Conditional Marketing Authorisation**
  - For **unmet medical needs** based on less comprehensive clinical data than usually required, often obtained in Phase 2
- **EMA & FDA: Accelerated Assessment and Priority Review**
  - Programs to expedite the review and approval process for therapies that show substantial benefit in early clinical data

Accelerated approvals granted

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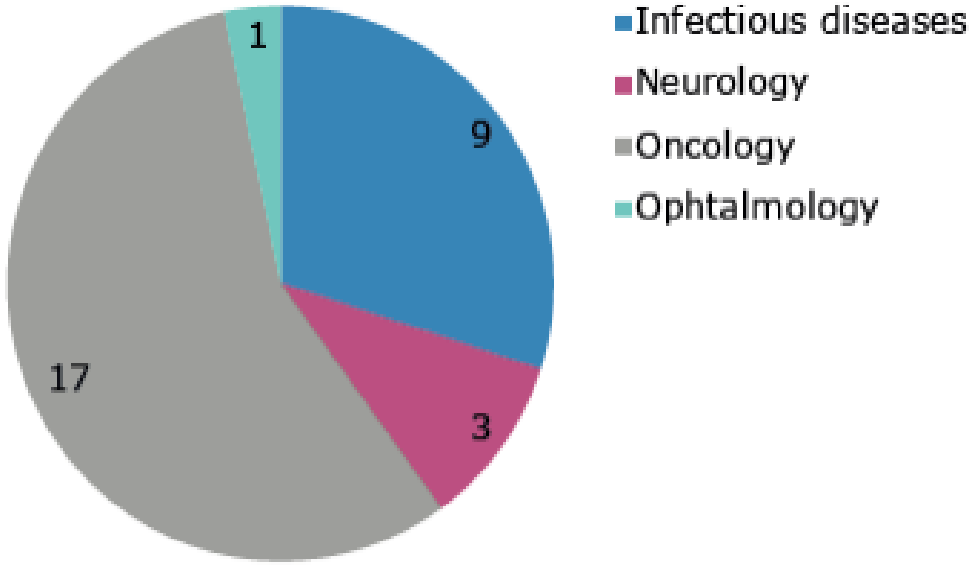
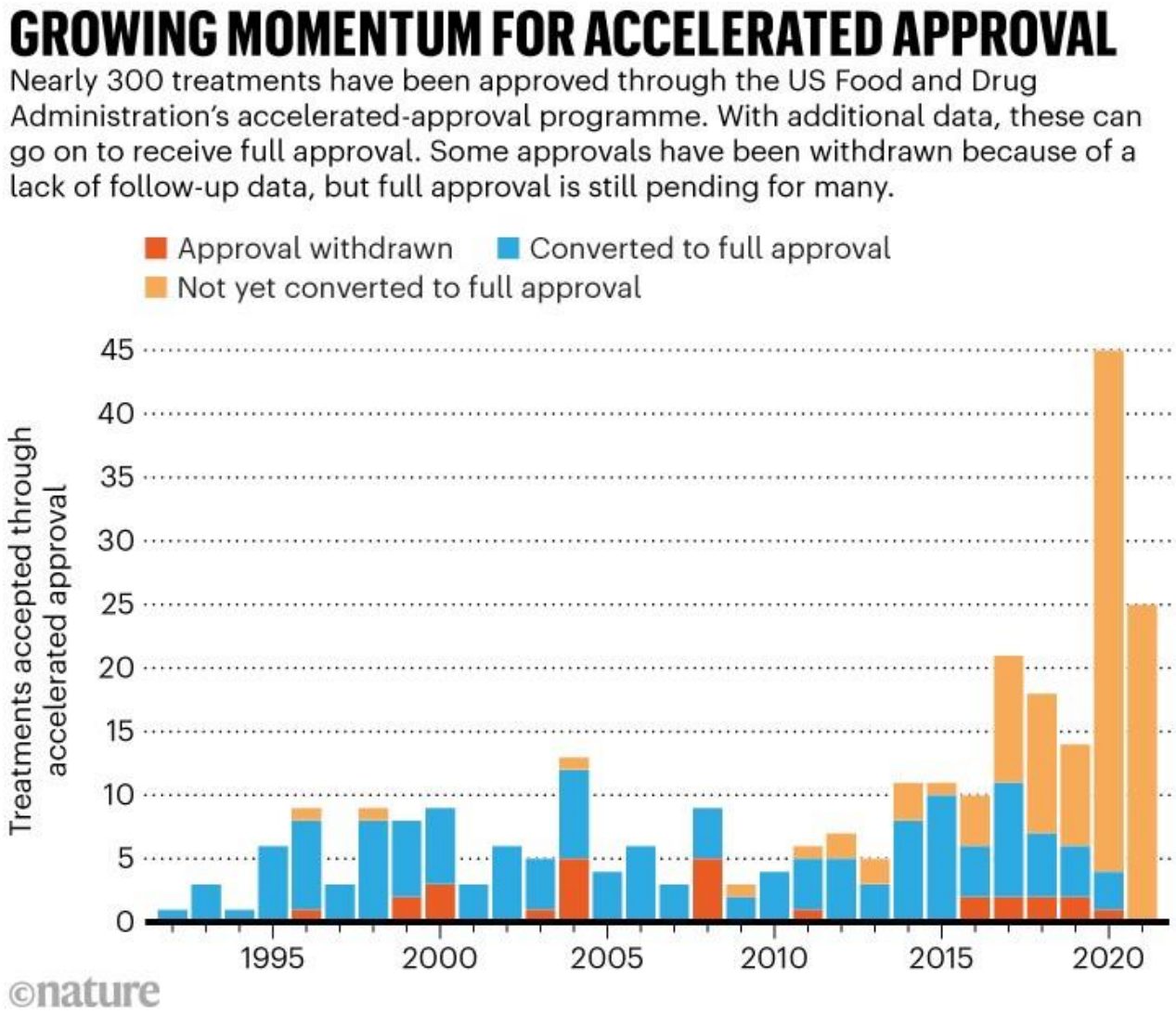
- ~300 approvals granted
- Growing interest over the years
- 4 therapeutic areas of high medical need *(2006–2016 EMA-granted approvals)*





Accelerated approval: *good, bad or ugly?*

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3 Experts Have Resigned From An FDA Committee Over Alzheimer's Drug Approval

UPDATED JUNE 11, 2021 · 7:04 PM ET

By Bill Chappell

Dr. Aaron Kesselheim (left), a professor at Harvard Medical School, at a documentary film screening in 2018 in Boston. He has resigned from a Food and Drug Administration advisory panel over the FDA's decision to approve an Alzheimer's drug.
Scott Eisen/AP Images for AIDS Healthcare Foundation

Three experts have now resigned from a Food and Drug Administration advisory committee after the agency approved an Alzheimer's drug called Aduhelm against the wishes of nearly every member on the panel.

BIOTECH

STAT+

Top FDA official Peter Marks overruled staff, review team to approve Sarepta gene therapy

By Jason Mast and Matthew Herper June 20, 2024

Reprints

Peter Marks, director of the Center for Biologics Evaluation and Research at the Food and Drug Administration.
JIM LO SCALZO/POOL/AFP VIA GETTY IMAGES

Key requirement for successfully applying the acc. approval pathway

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Measurement of levels of any kind have to provide insight into a pharmacologic effect on a biomarker in the pathway of the disease

Strategies to shorten your development pathway **– case 2**

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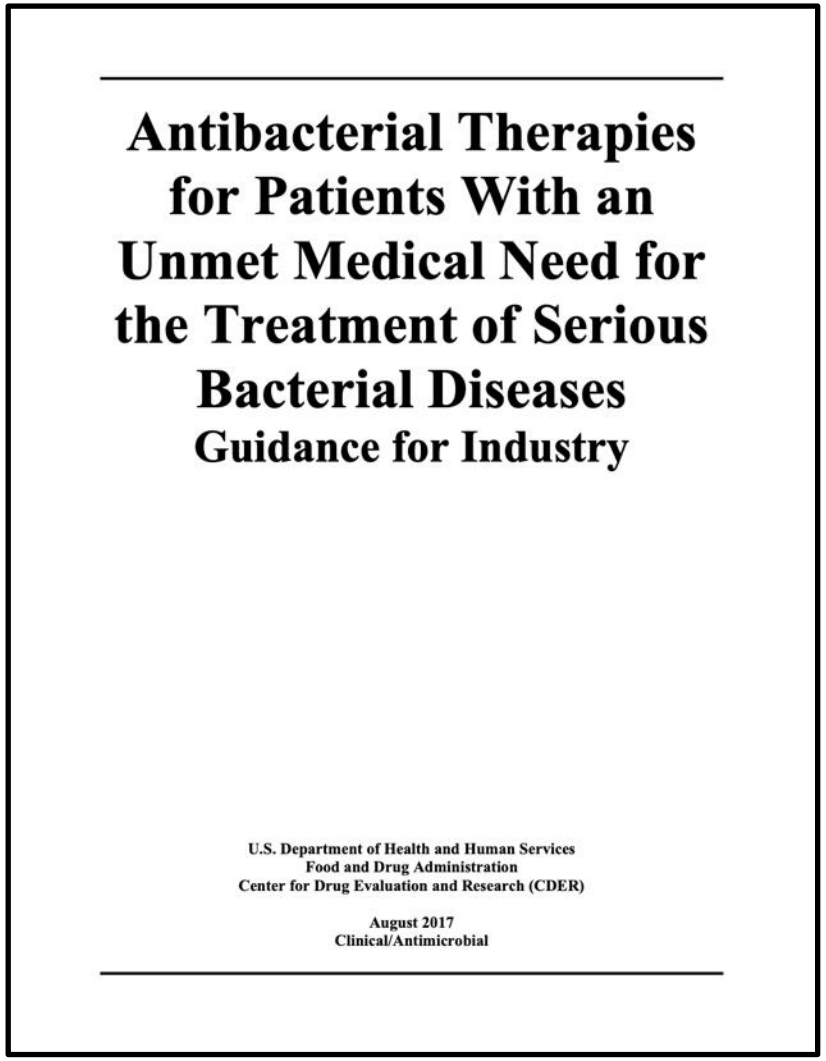
- Client X having 3 programs for different infectious diseases in their pipeline
  - All in phase I/IIA
  - What to do with them? stop/continue/change?
- 4 steps
  1. Detailed analysis of all 3 programs
  2. Redefined the target product profiles
  3. Smart program design
     1. resulted in a reduction of the program cost from **200M to 70M** for one program
  4. Calculate the rNPV with and without smart design



Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2017
Clinical/Antimicrobial

Conclusions

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- "Unmet medical need" is a cornerstone to shorten your development pathway
- Your data need to look great!
- Biomarkers play an essential role
  - Start early if you are in an underdeveloped indication
  - Incorporate validation into your trial design in this case
    - *by bridging biomarkers to traditional clinical endpoints*
  - Be prepared to adapt your clinical strategy, if needed

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