Translational Research in the Context of the Changing Dynamics of Biopharmaceutical Innovation

Prepared for: Todai

Tokyo, February 1st, 2017

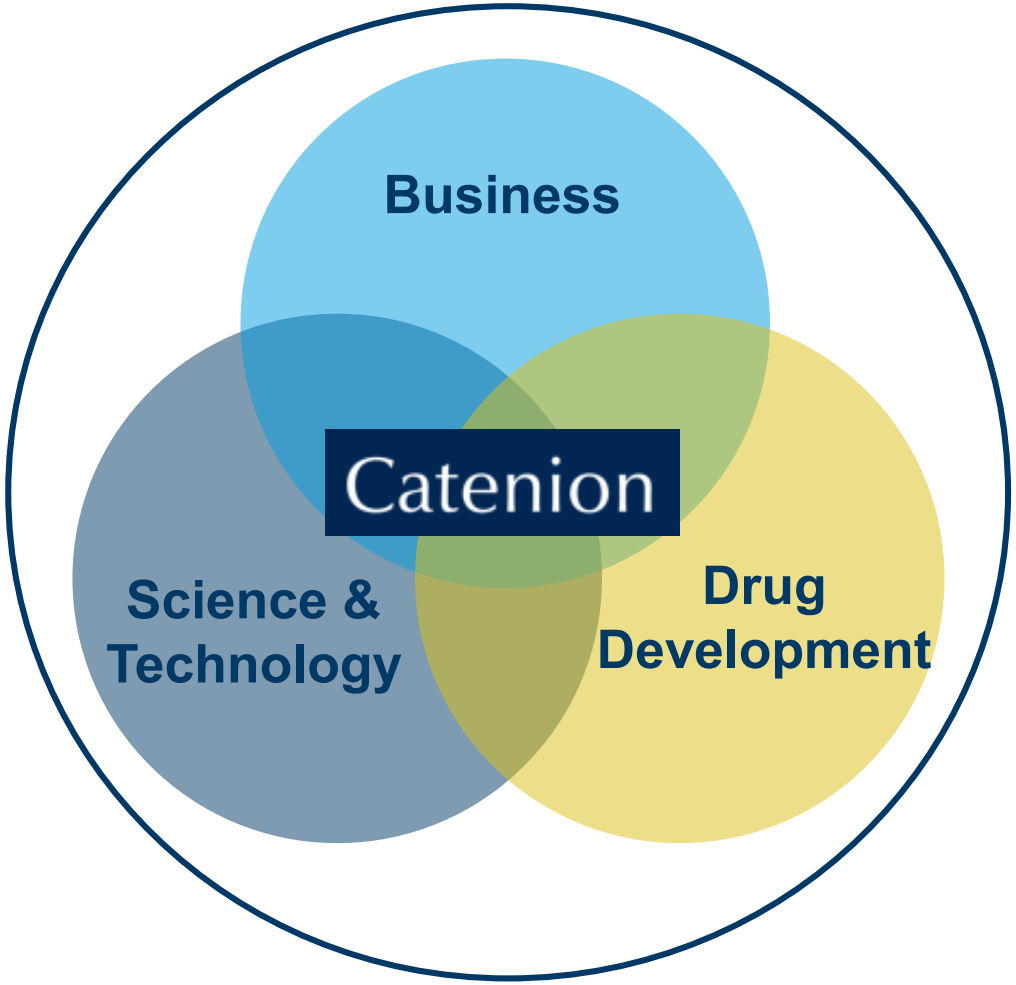
Catenion

Agenda

- **By Way of Introduction**

Working primarily for Biopharma, Catenion has a proven track record of creating value for clients and patients

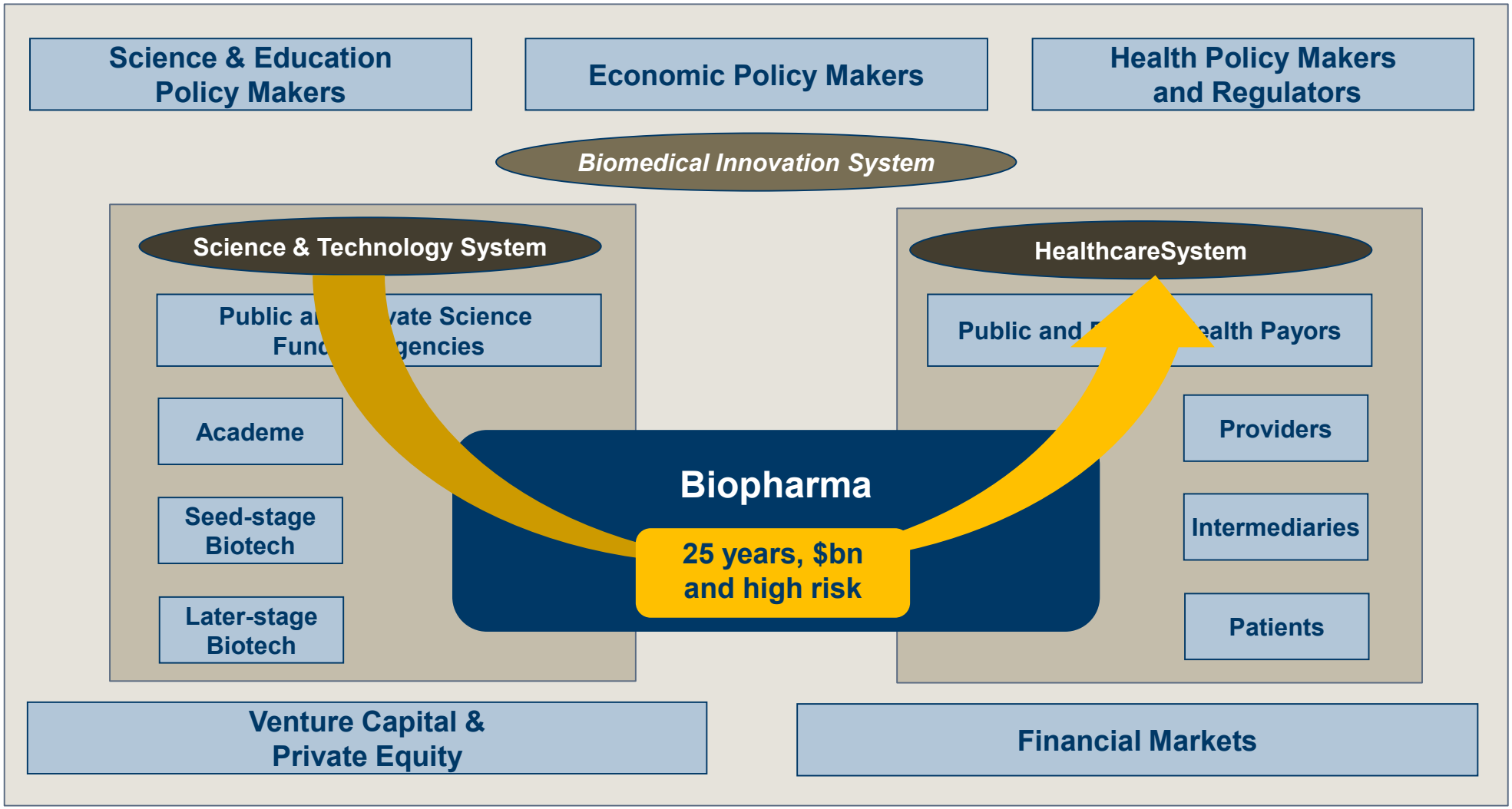
- Largest team exclusively focused on Biopharma R&D
- Objectivity and independent thought
- Assessed >1,000 projects, often in collaboration with R&D project teams



- Helped develop more than 10 marketed drugs
- Value creation through portfolio strategy and optimization
- Trusted partners of top executives in Europe, the US and Japan

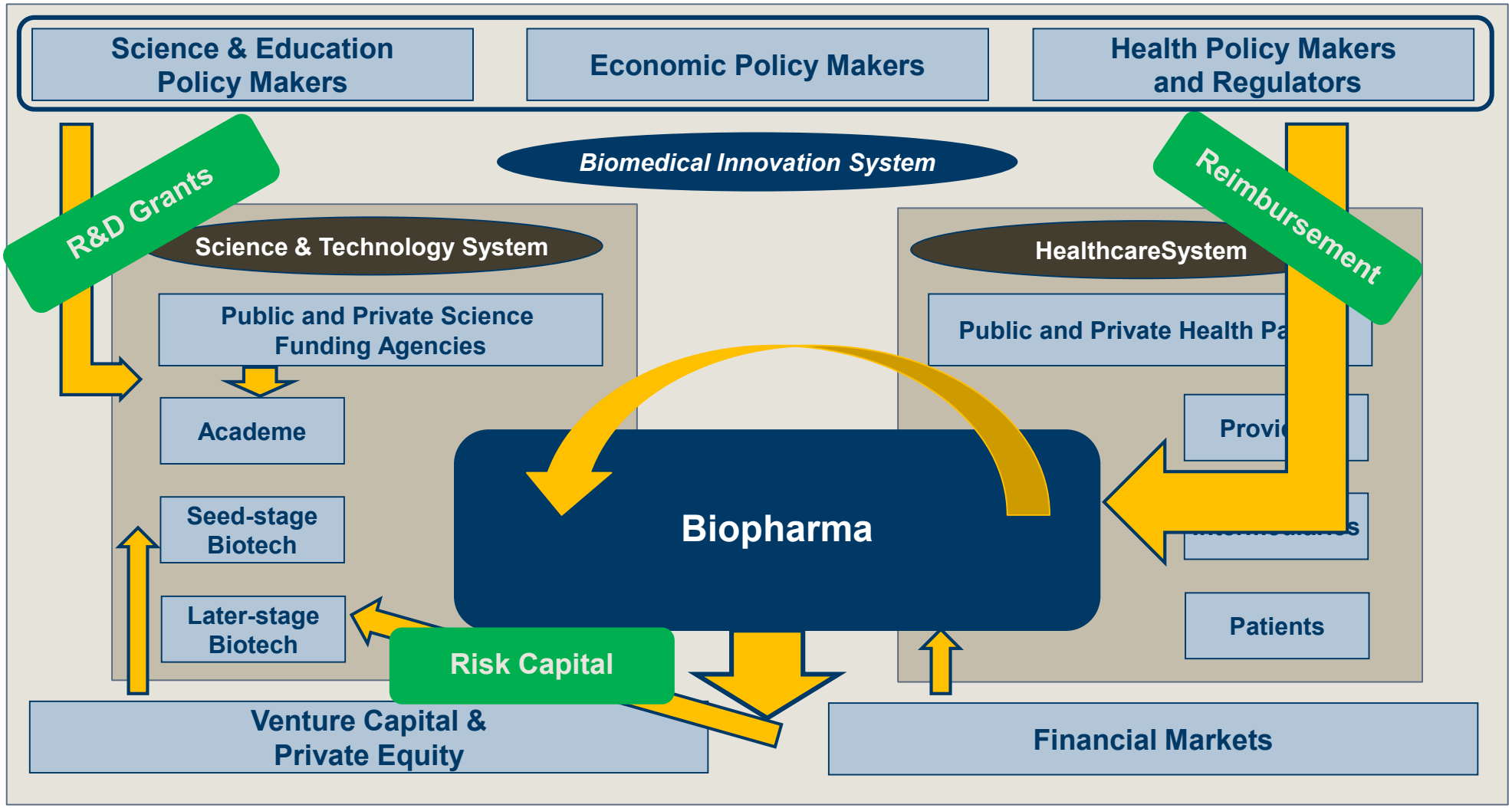
Source: Catenion

It is sometimes useful to remind ourselves of the context within which biopharma operates: Science, technology, healthcare, as well as rules and regulations: The "Biomedical Innovation System"



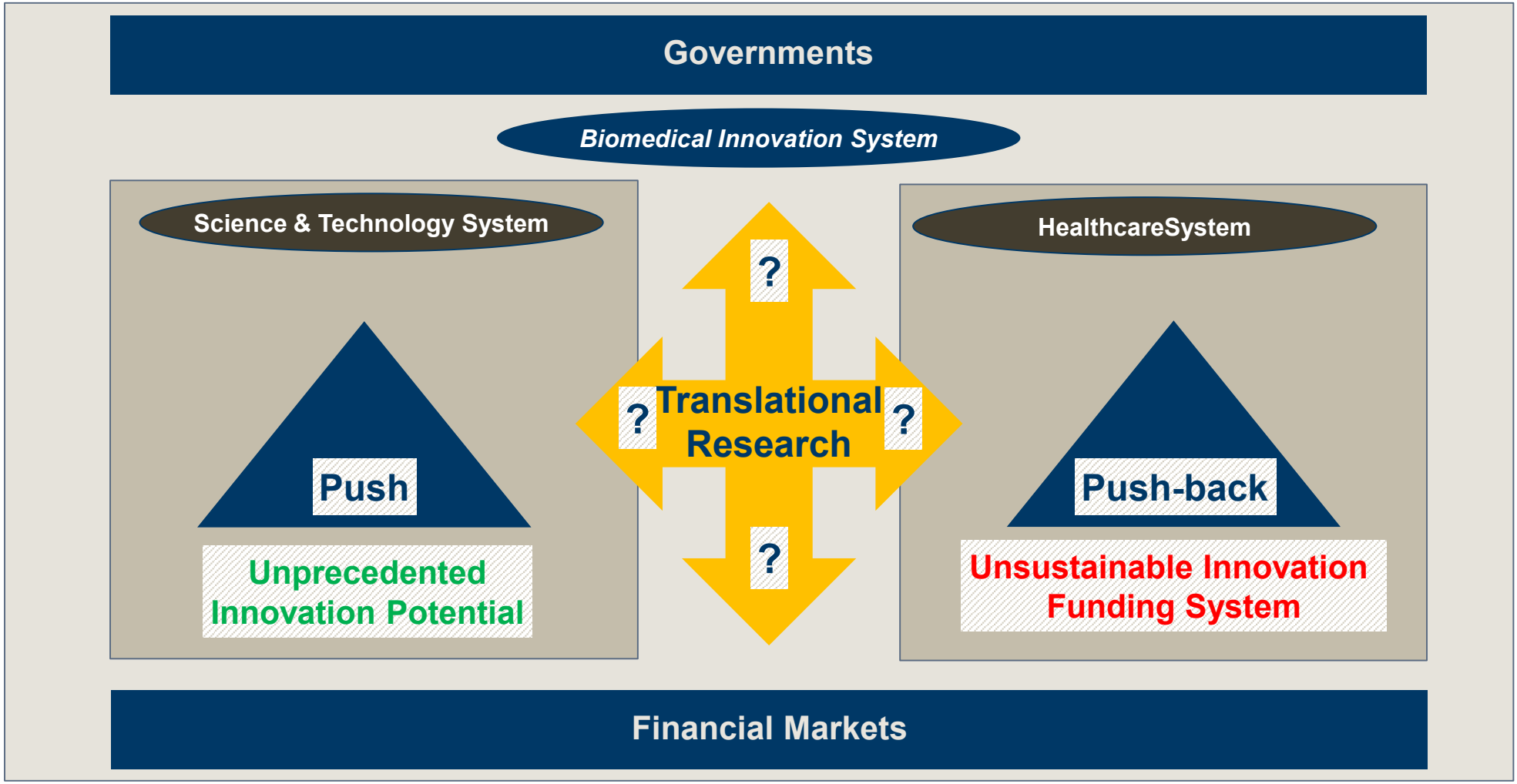
Source: Catenion

The funding mechanisms for innovation in this "Biomedical Innovation System" are often taken for granted



Source: Catenion

The main hypothesis of this presentation: Current trends are putting Translational Research at centre stage and will change business models of all players

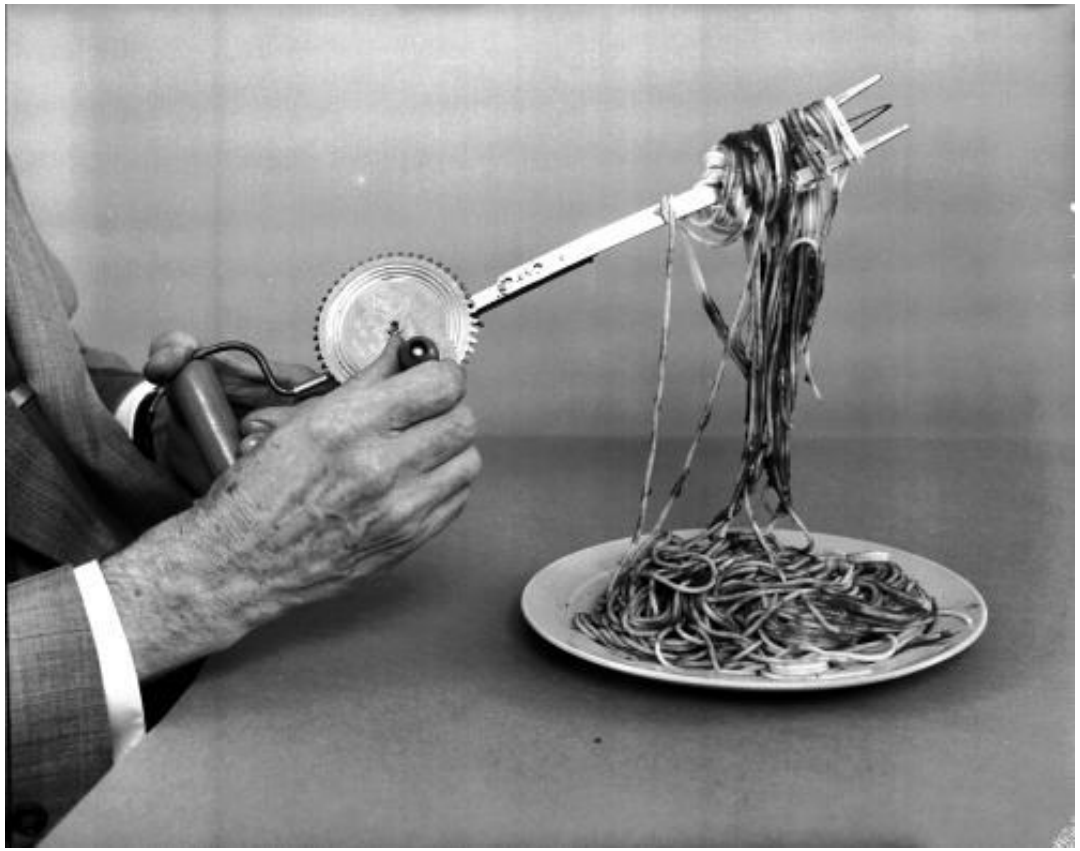


Source: Catenion

Agenda

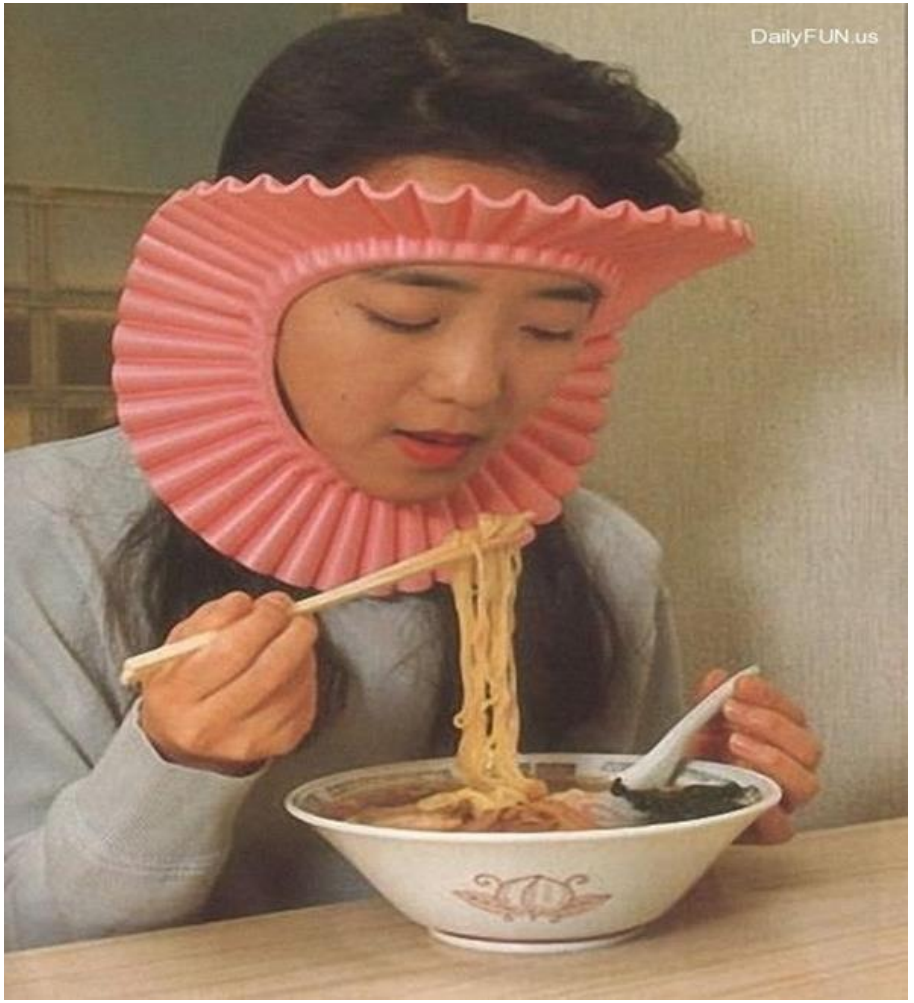
- **What is Biopharma Innovation and What Are We Measuring?**
- Biopharma Innovation Cycles
- Changing Roles of Different Players in Translational Research and Innovation
- Brief Summary

Innovation is not the same thing as invention – for an invention to become an innovation, it needs to be adopted into practice



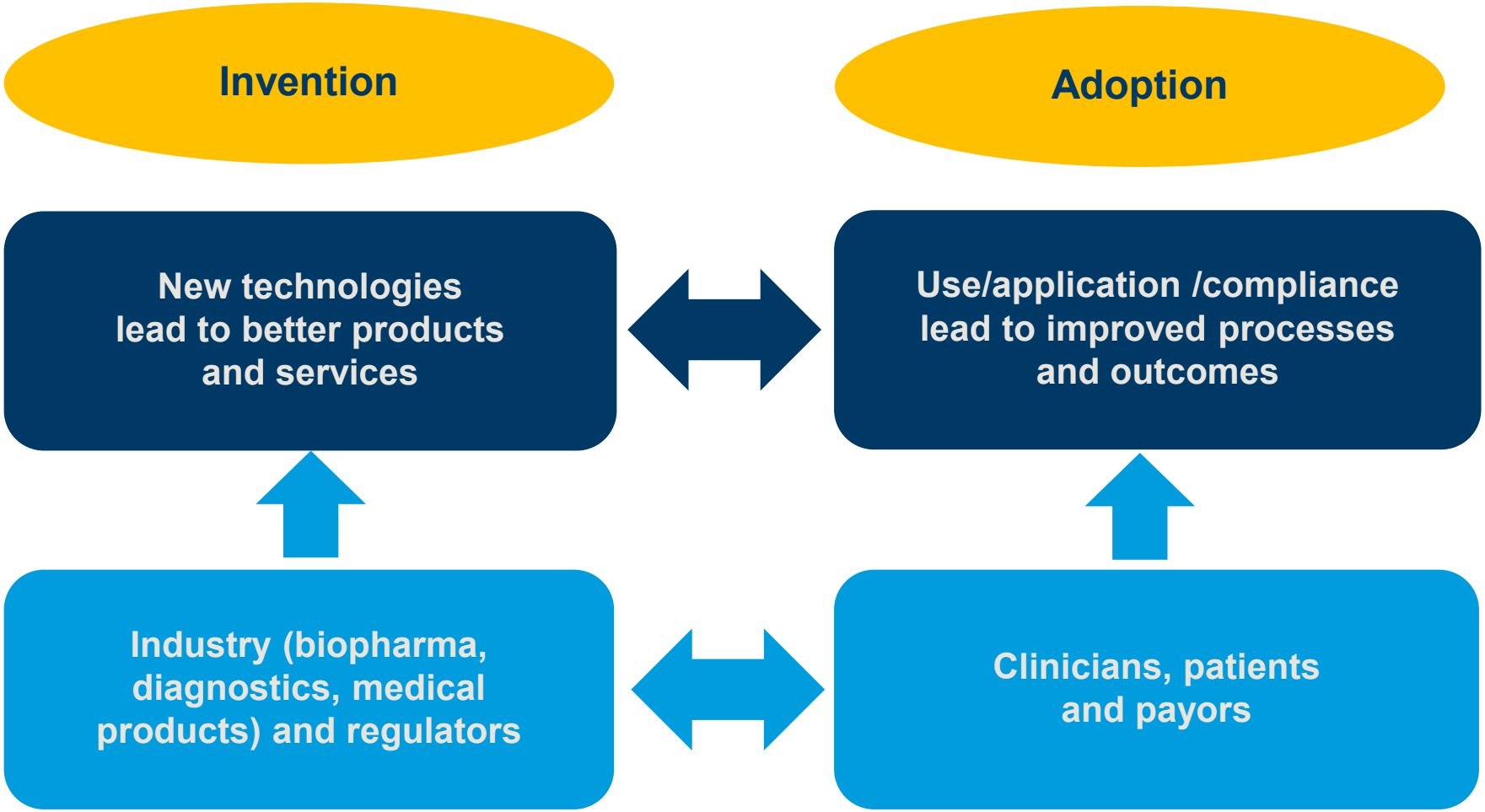
Source: http://www.ebaumsworld.com/pictures/view/81768615/;
https://www.google.com/search?q=failed+inventions&biw=1186&bih=613&source=lnms&tbm=isch&sa=X&ved=0CAYQ_AUoAWoVChMIk8C5urzCyAIVgTs-Ch1mZQbI#imgrc=OMRCSzcNNQB5gM%3A

Not all creative ideas have proven to be practical



Source: http://www.ebaumsworld.com/pictures/view/81768615/;
https://www.google.com/search?q=failed+inventions&biw=1186&bih=613&source=lnms&tbm=isch&sa=X&ved=0CAYQ_AUoAWoVChMIk8C5urzCyAIVgTs-Ch1mZQbI#imgrc=OMRCSzcNNQB5gM%3A

Biopharmaceutical innovation requires R&D at the front end (invention) and translation into clinical practice at the back end (adoption) – multiple players have to co-operate for this to happen



Source: Catenion

Invention saves lives – Strimvelis, lentivirus-based ex vivo stem cell/ gene therapy for ADA-SCID (adenosine deaminase deficiency severe combined immuno-deficiency)

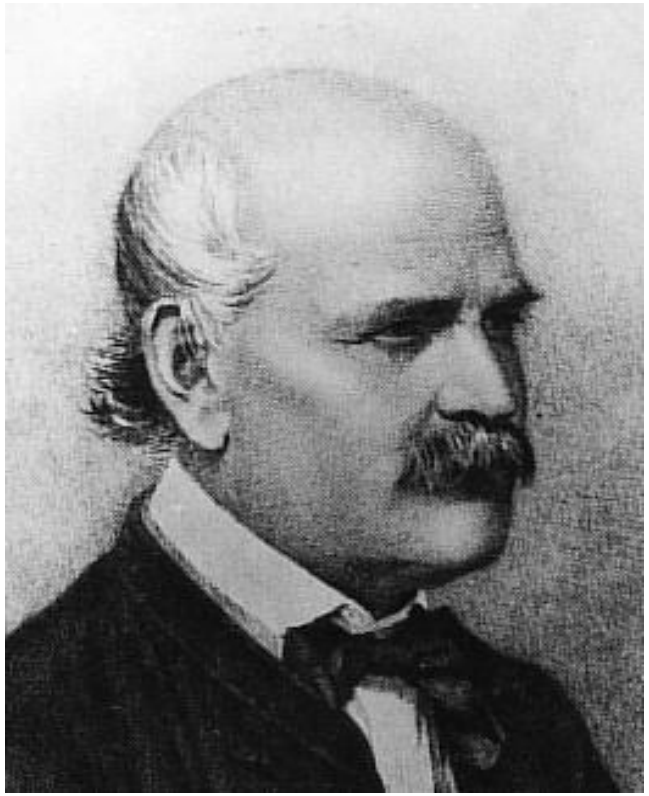
Bubble Boy

- **58 patients treated, first treated patient still alive and well after 13 years**
- **Approved by EMA in 2016**

Source: Catenion

Adoption saves lives, too but it can take time - the story of Ignaz Semmelweiss - Hand-washing by doctors and nurses dramatically reduces death rates in obstetric yards

Late 1840‘s



2015

Source: Catenion

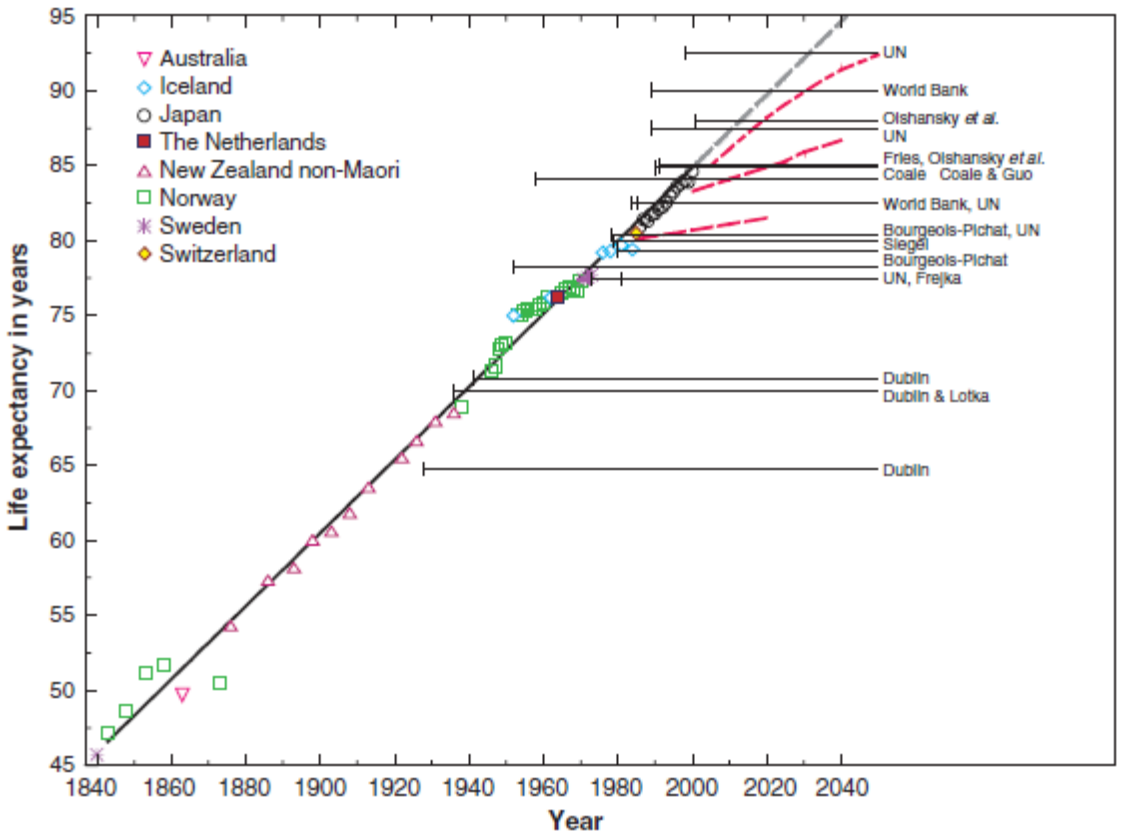
How can we measure the impact of innovation on medicine over time?

Life Expectancy would be a first choice parameter

Source: Catenion

„For 160 years, best-performance life expectancy has steadily increased by a quarter of a year per year, an extraordinary constancy of human achievement“

Record Female Life Expectancy from 1840 to the Present



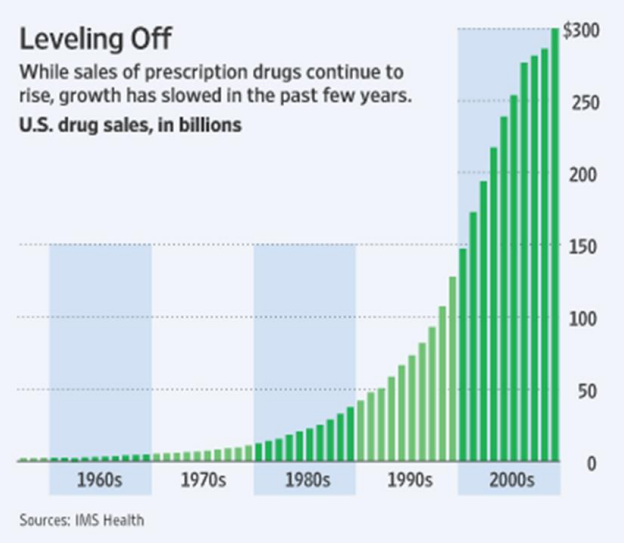
Start of
- „Modern Medicine“ around 1900
- „Modern Rx Industry“ around mid-1930‘s

Why is there no visible effect on survival?

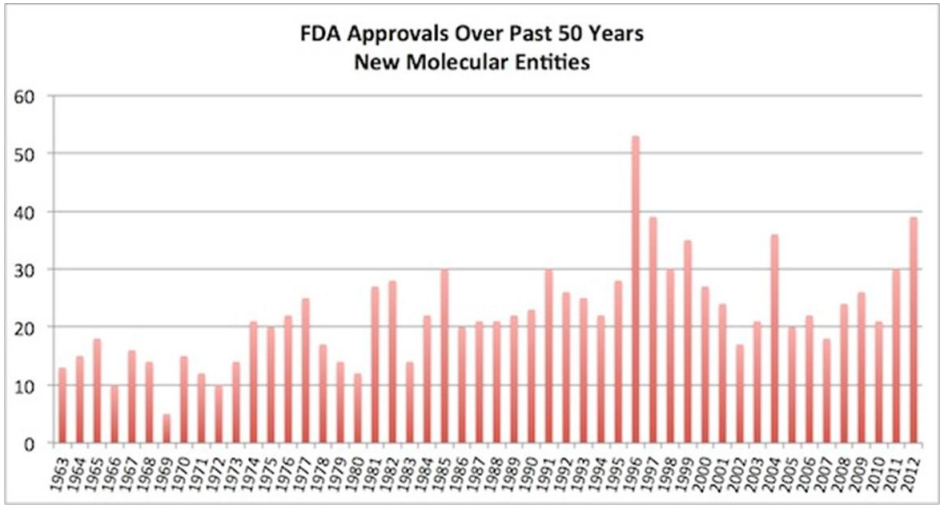
Source: Jim Oepen, James W. Vaupel: Broken Limits to Life Expectancy in: Science Vol 296 10 May 2002

If Life Expectancy were a direct function of biomedical innovation, then innovation would have to be represented by a straight, upwards sloping line

Sales of Prescription Drugs



FDA Aprovals of NMEs

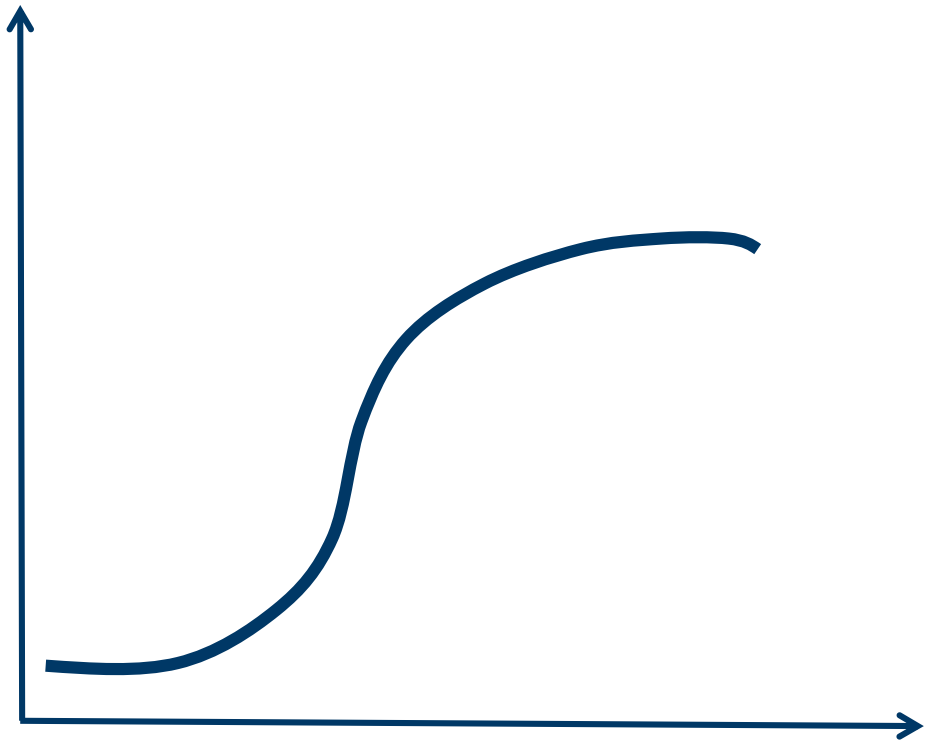


Major surrogate parameters do not look like straight lines at all and seem implausible as representations of biomedical innovation over time

Source: Catenion

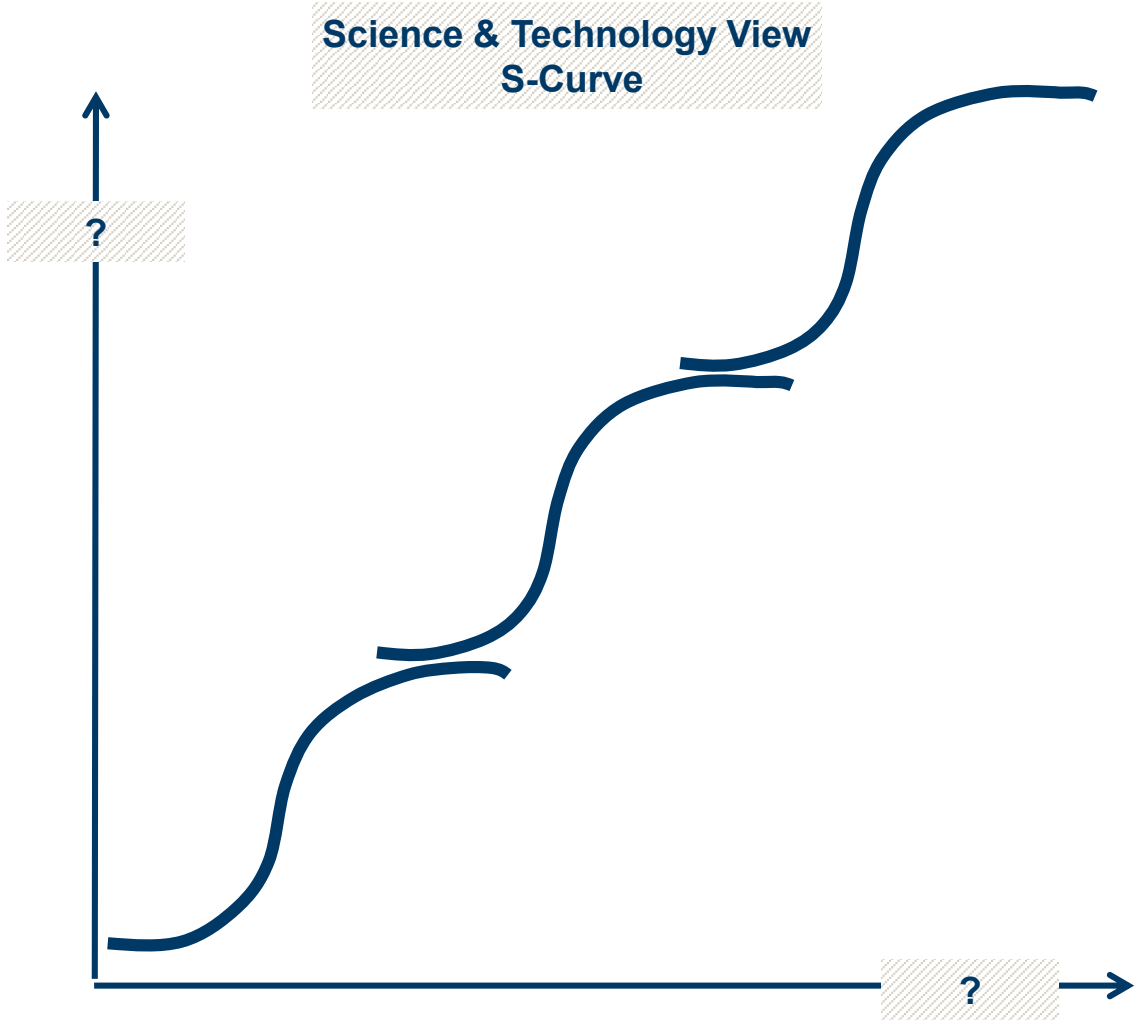
The original drivers of bio-medical innovation are to be found in the fields of Science & Technology, so the classic S-curve might be a good starting point

Science & Technology View
S-Curve



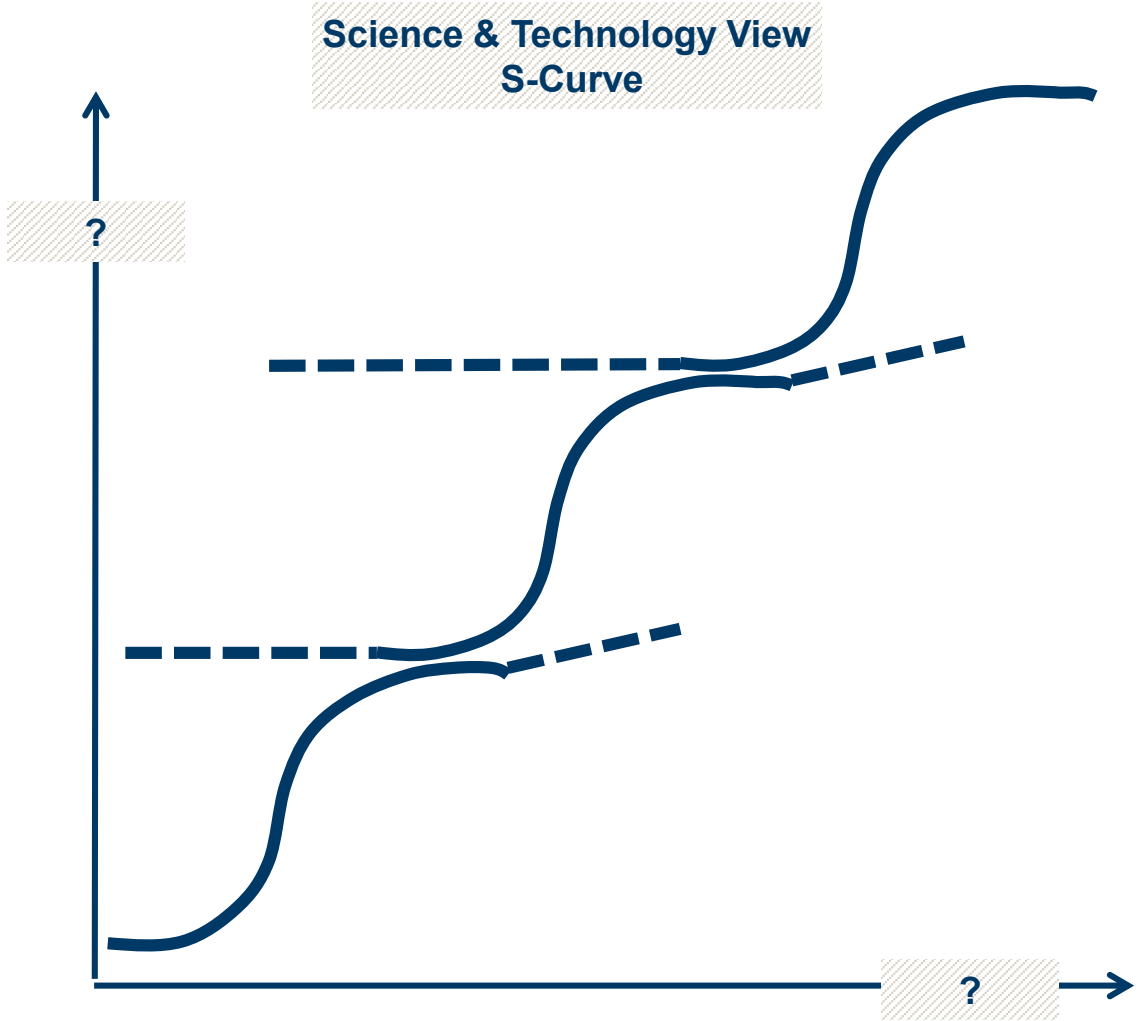
Source: Catenion

Also, we would expect a number of S-curves to follow and supersede each other in time..



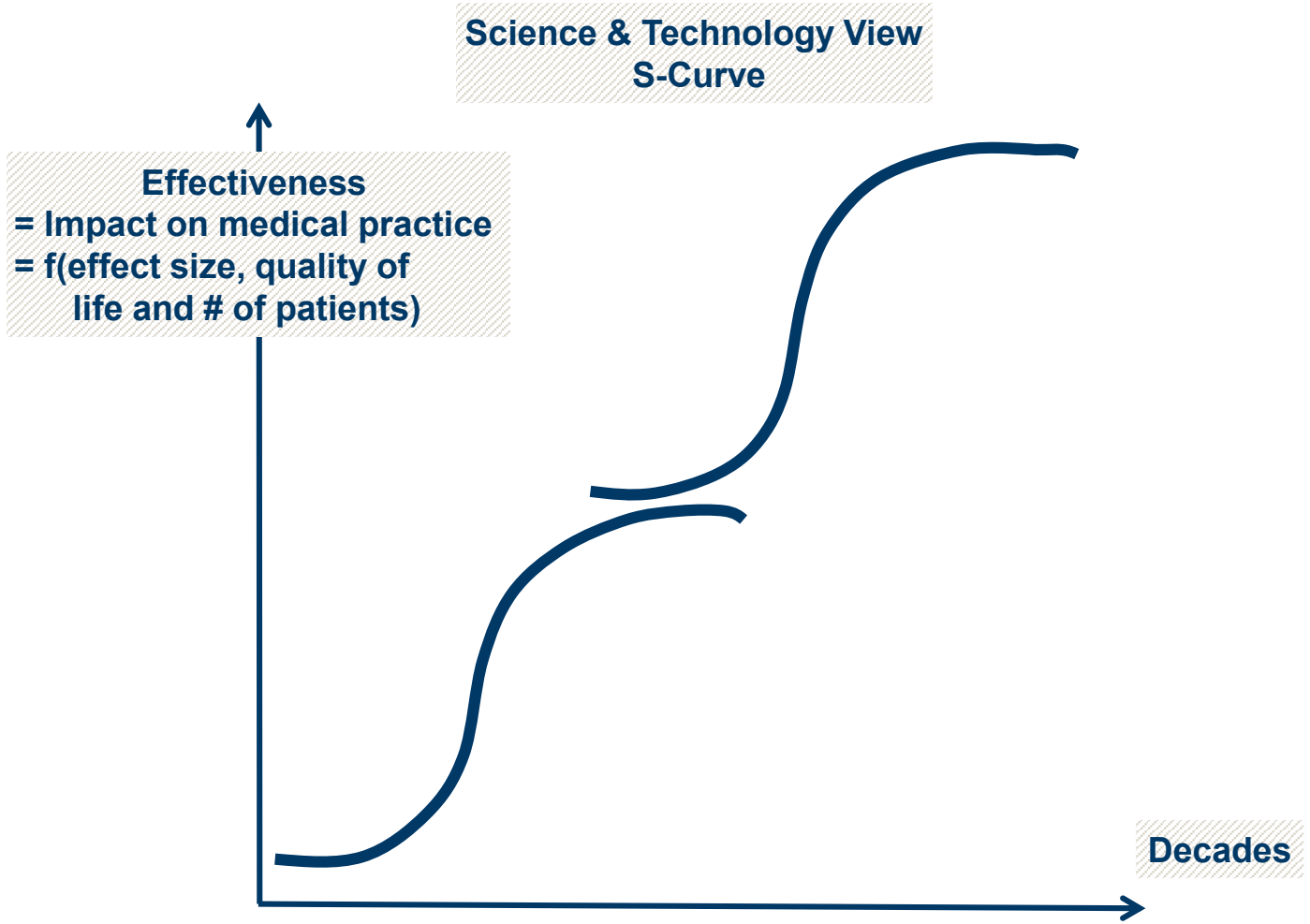
Source: Catenion

New curves have very long lead times before they mature and incremental innovation continues to take place on the „old“ S-curve in parallel to breakthtoughs on the new one



Source: Catenion

But what measure can we use for the y-axis? Clearly, life expectancy does not do the job – and no other single parameter will either, so we need a composite qualitative index

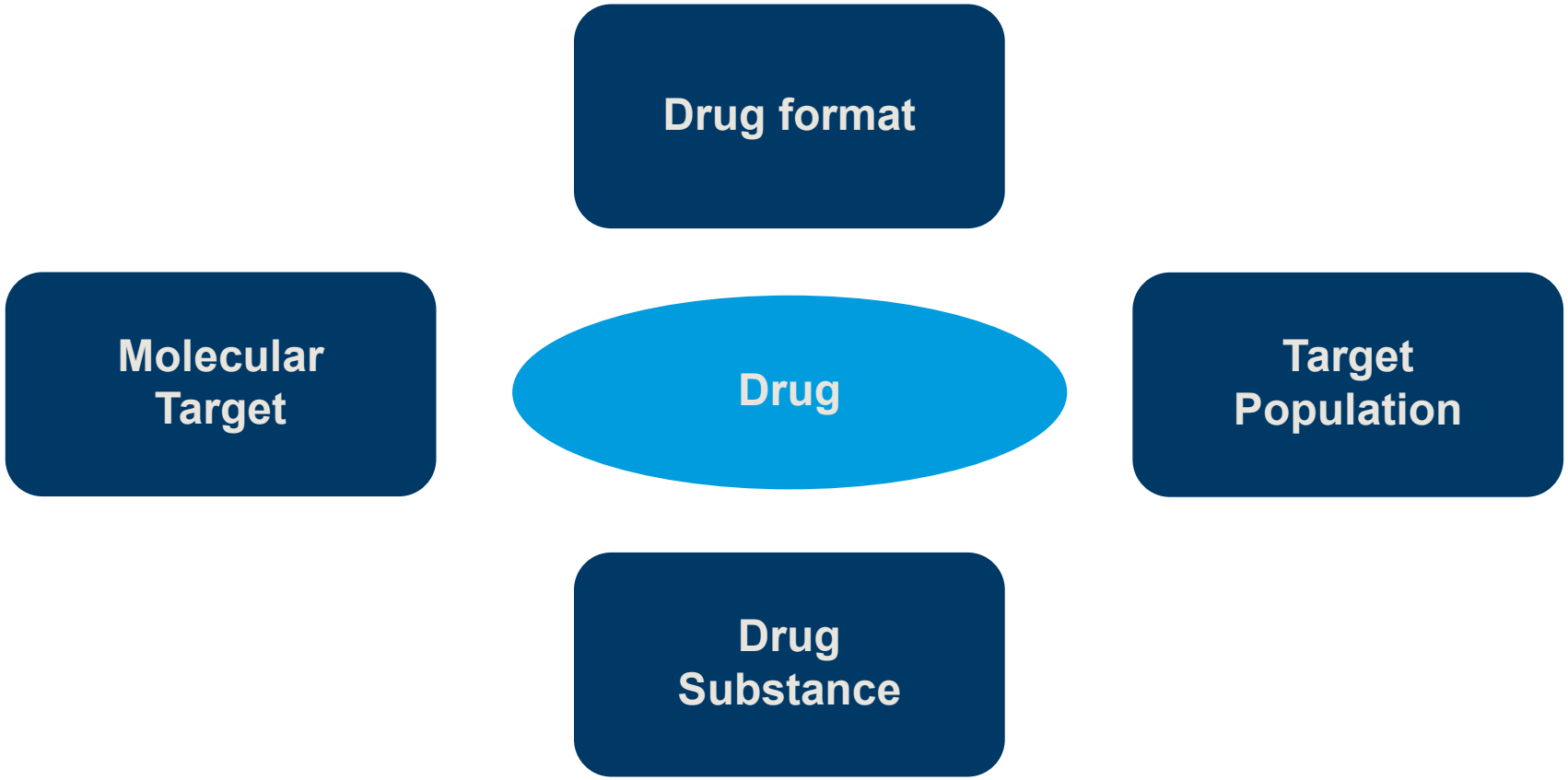


Source: Catenion

Agenda

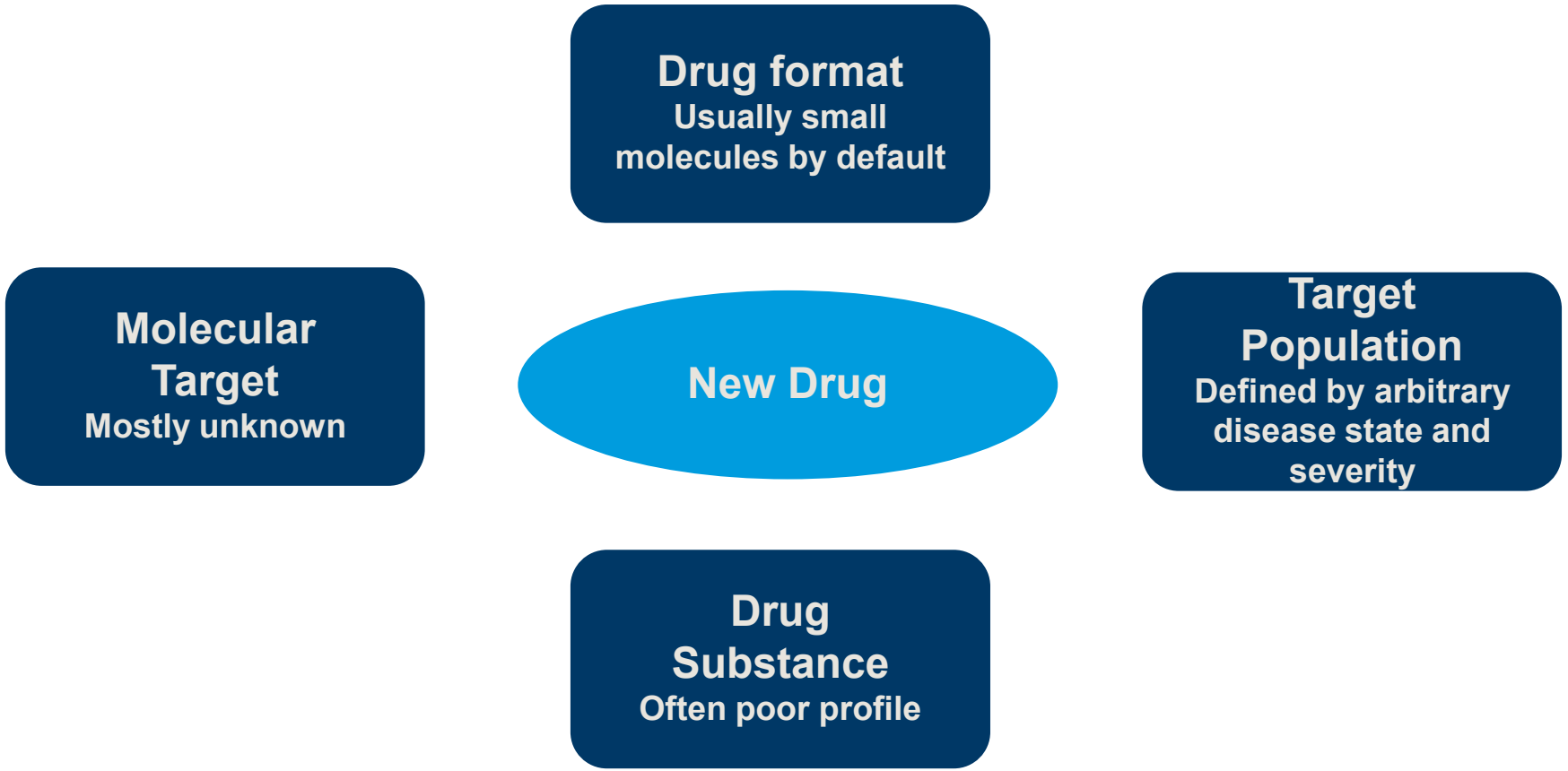
- What is Biopharma Innovation and What Are We Measuring?
- **Biopharma Innovation Cycles**
- Changing Roles of Different Players in Translational Research and Innovation
- Brief Summary

To make a new drug, four basic dimensions must be addressed



Source: Catenion

In this famework, bio-pharmaceutical innovation as represented by the first S-curve from the 1930s onwards was essentially driven by what might be called „Pure Phenotypic Discovery“…



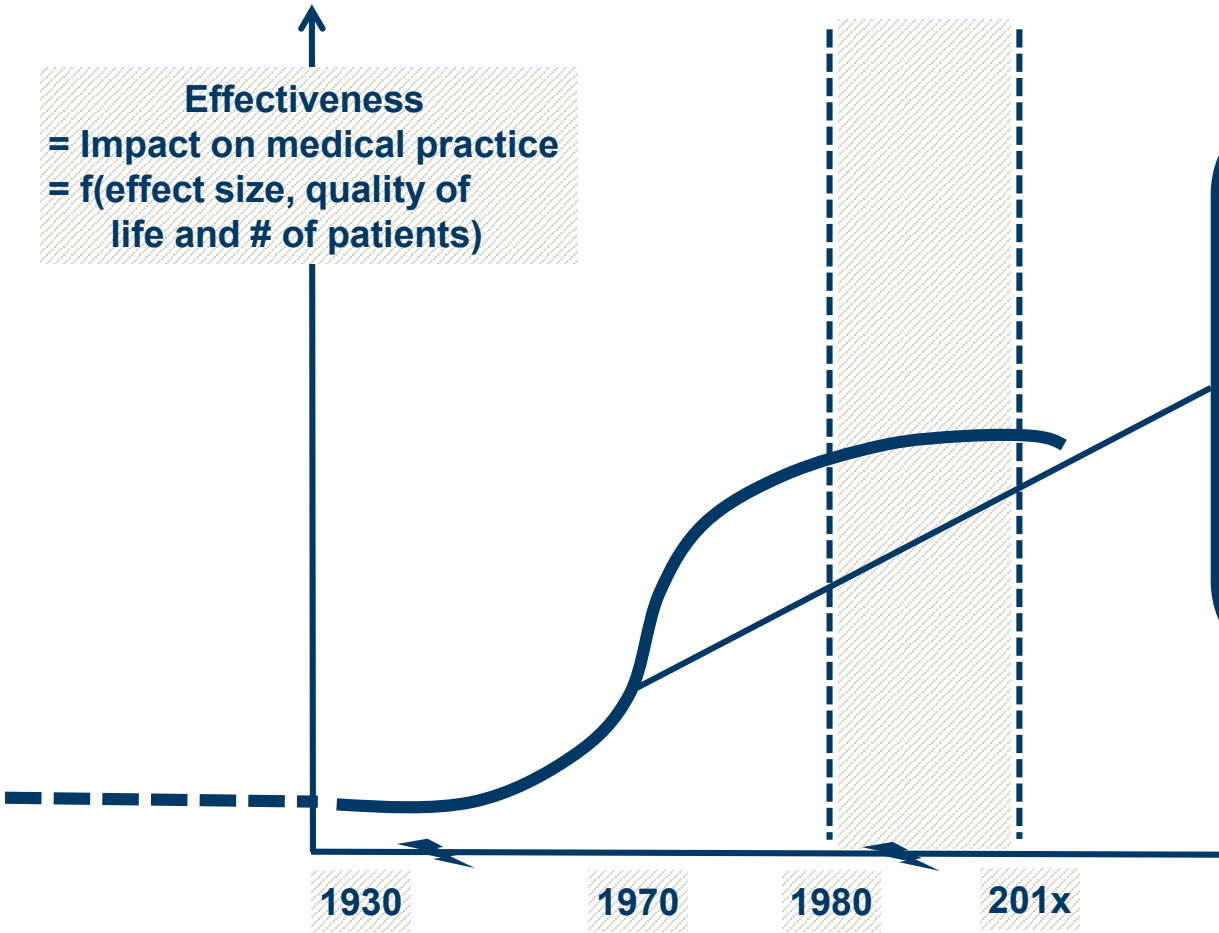
Source: Catenion

Bio-pharmaceutical innovation on the first S-curve: Phenotypic discovery by trial and error and straightforward clinical development

- **Contribution of many different disciplines, but limited exploratory clinical research**
- **Sometimes translational insights in the clinic**

Source: Catenion

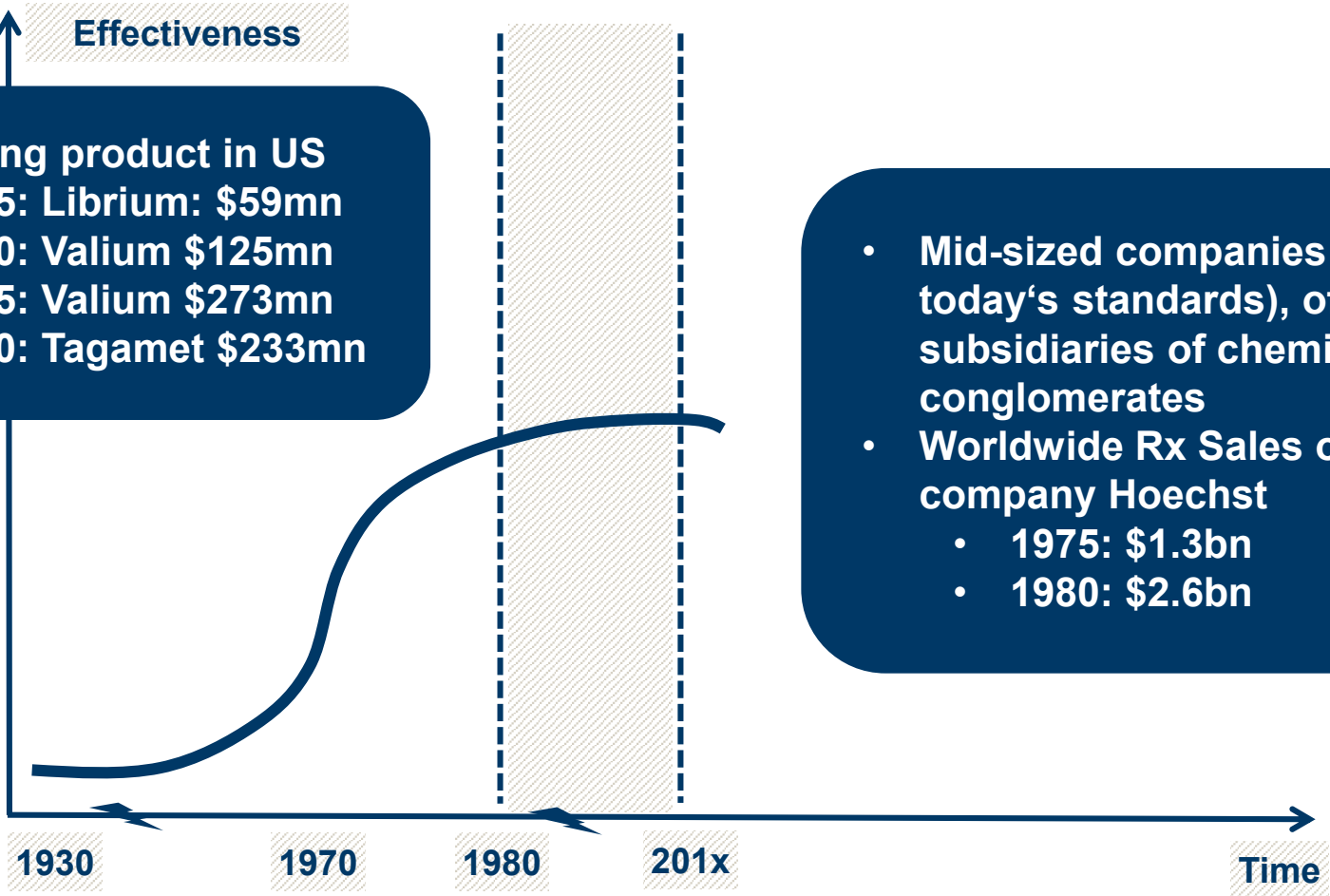
The first pharma S-curve – starting to take off in the 1930s with sulfa drugs and rapidly accelerating in the 1940s, then peaking in the 1950s and 60s



- Many new drug classes, among them: sulfa drugs, anti-infectives, hormones, vitamines, immuno-suppressants, psychotropics, hypoglycemics, first cytotoxics and many more
- Prescription drugs as a % of all medicines in US
  - 1929: 32%
  - 1969: 83%

Source: Catenion Research, National Research Council: The Competitive Status of the US Pharmaceutical Industry, 1983; http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm

The first 50 golden years – massive innovation, small sales per product, mid-sized companies – no VCs/ no biotechs/no Big Pharma...

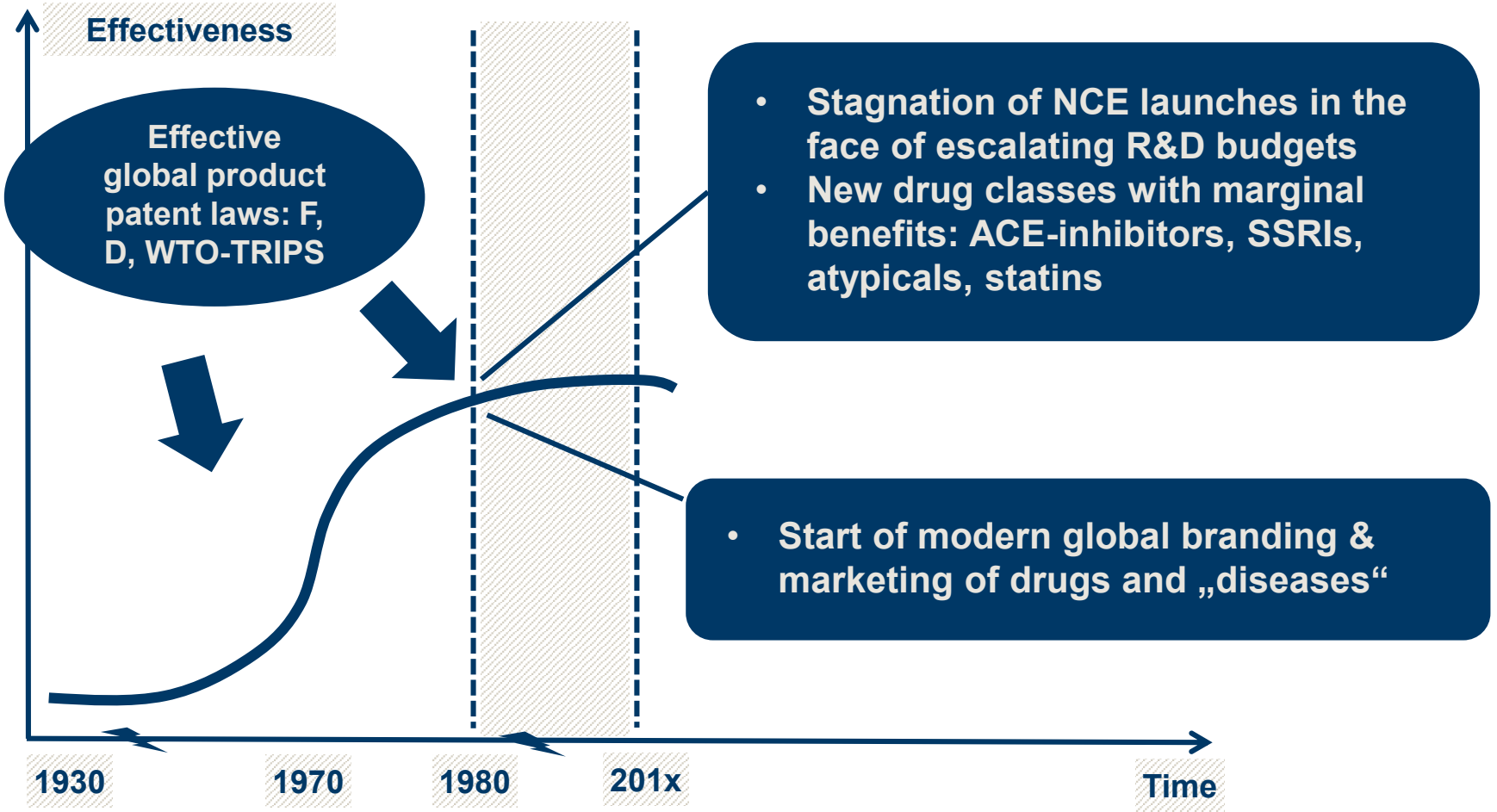


- Top-selling product in US
  - 1965: Librium: $59mn
  - 1970: Valium $125mn
  - 1975: Valium $273mn
  - 1980: Tagamet $233mn

- Mid-sized companies (by today's standards), often subsidiaries of chemical conglomerates
- Worldwide Rx Sales of top company Hoechst
  - 1975: $1.3bn
  - 1980: $2.6bn

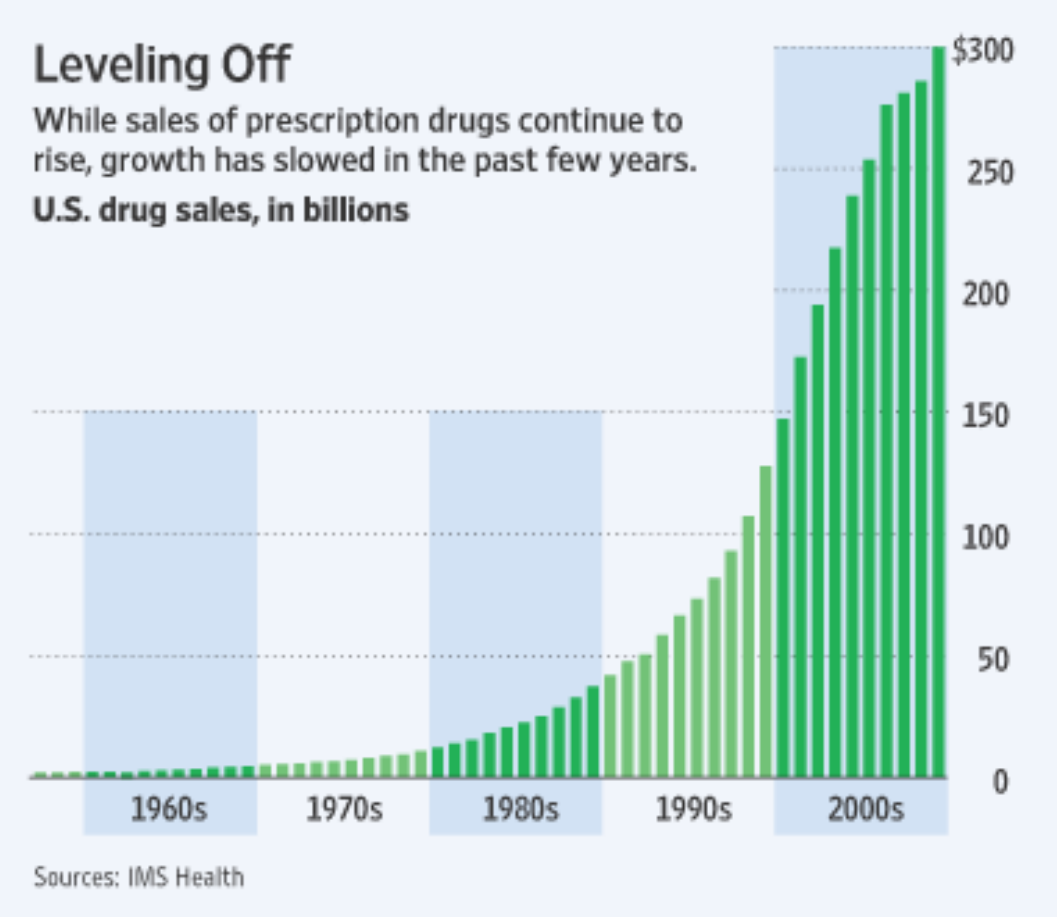
Source: Catenion Research, National Research Council: The Competitive Status of the US Pharmaceutical Industry, 1983

Stagnation from the mid-80s onwards – the slowing of innovation and the emergence of Big Pharma and blockbusters



Source: Catenion

Steep sales growth for pharmaceuticals in the US since the late 1980s - at a time when innovation was slowing down



Source: IMS

Industry consolidation as a sign of innovation decline: Of the PhRMA members active in 1988, by 2011 only one quarter remained active – all others had disappeared through M&A

PhRMA members active in 1988

Abbott Laboratories	G.D. Searle	Procter & Gamble
American Cyanamid	Glaxo	Rhone Poulenc
A.H. Robins	Hoechst	Rorer
Astra	Hoffmann-LaRoche	R.P. Scherer
BASF	ICI	Roussel
Beecham Laboratories	Johnson & Johnson	Sandoz
Boehringer Ingelheim	Knoll	Schering Plough
Boots Pharmaceuticals	Eli Lilly	SmithKline
Bristol-Myers	Marion Laboratories	Squibb
Carter-Wallace	Merck	Sterling Drug
Ciba Geigy	Merrell Dow	Upjohn Company
Connaught Laboratories	Monsanto	Warner-Lambert
DuPont Pharmaceuticals	Pfizer	Wellcome
Fisons	Pharmacia	Zeneca

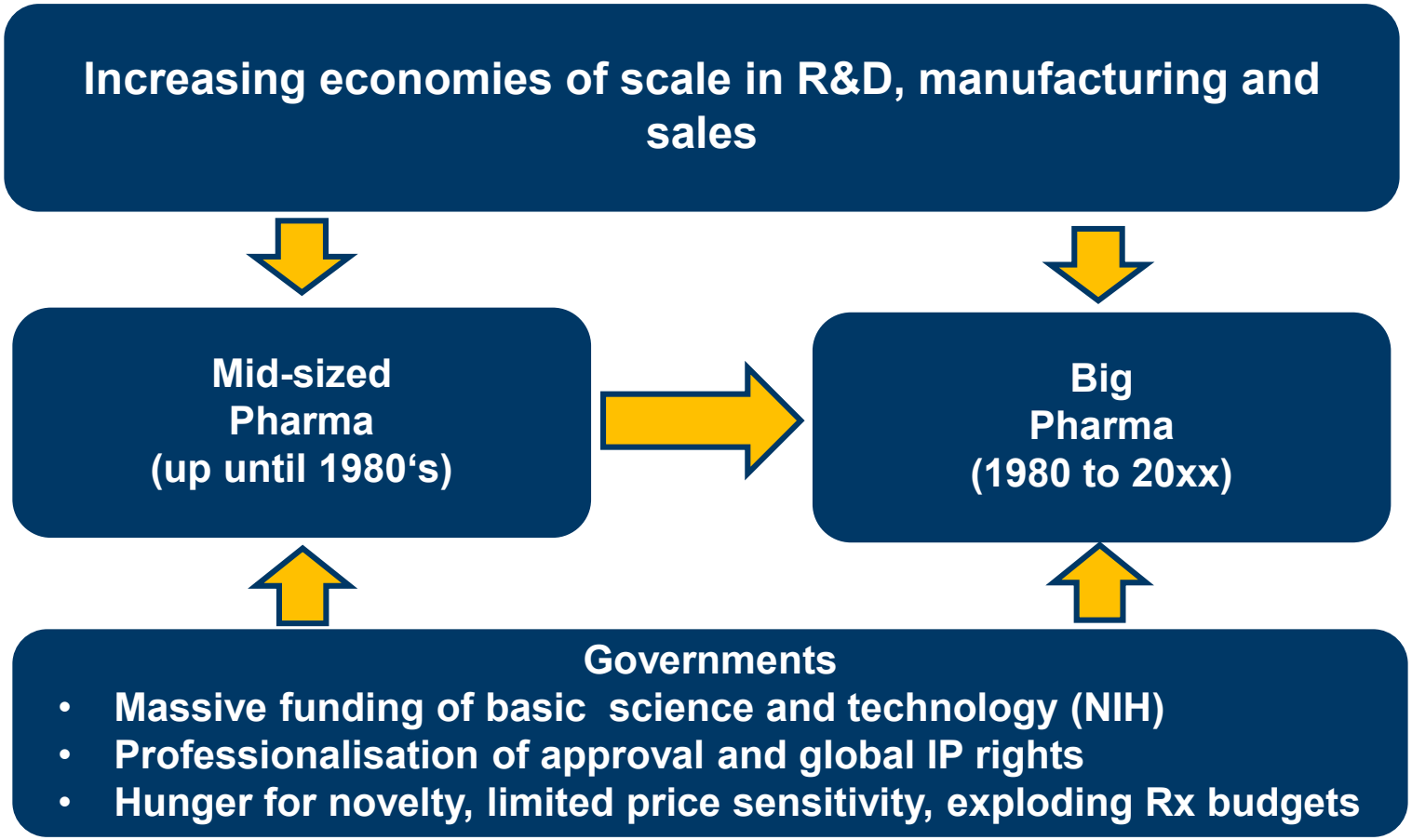
PhRMA members remaining in 2011

Abbott Laboratories	Eli Lilly
AstraZeneca	Merck
Boehringer Ingelheim	Novartis
Bristol-Myers Squibb	Pfizer
Glaxo SmithKline	Sanofi-Aventis
Johnson & Johnson	

25%

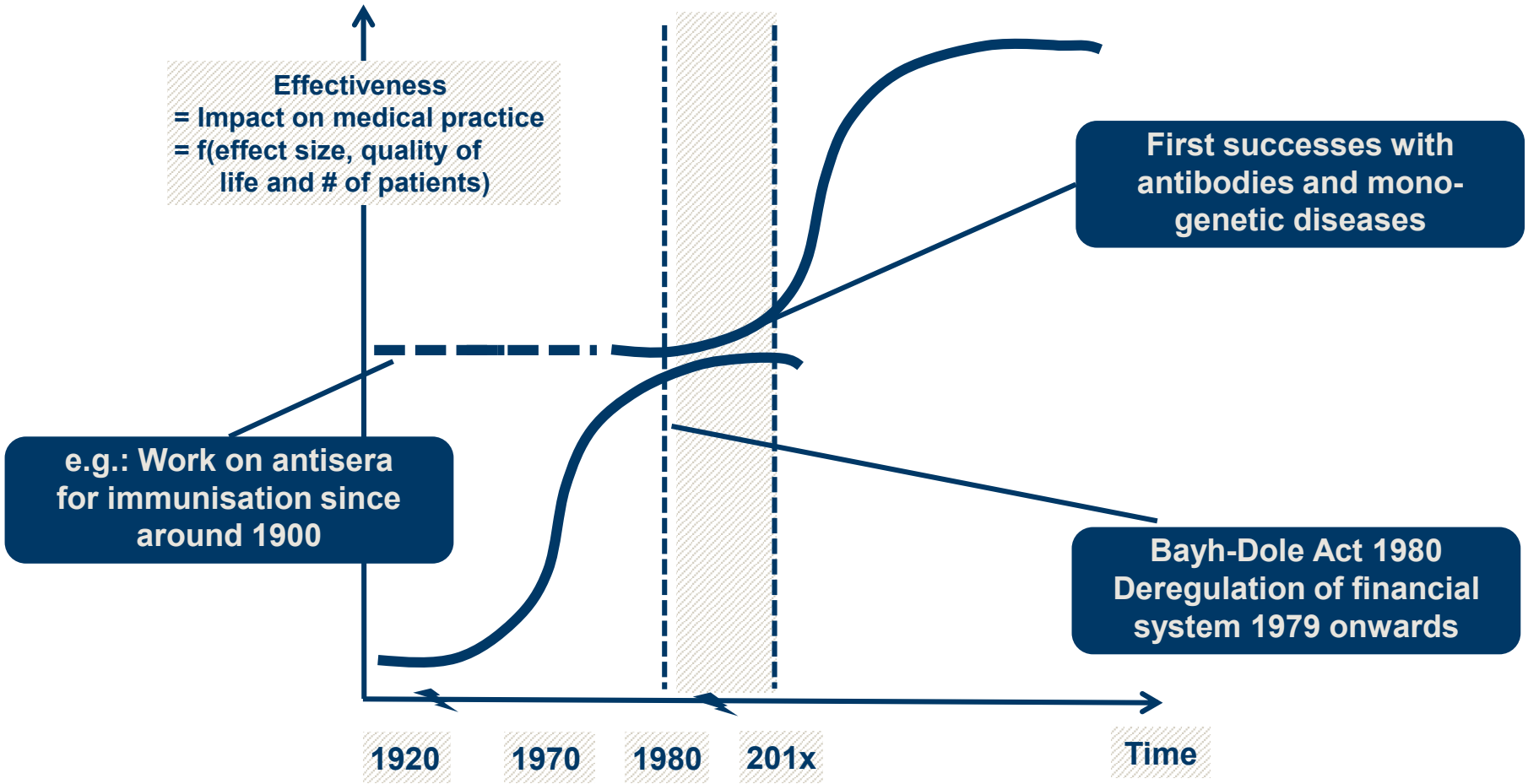
Source: *John L. LaMattina,* The impact of mergers on pharmaceutical R&D in Nature Reviews Drug Discovery, Vol 10, Aug 2011

Big Pharma emerged driven by flattening innovation curve, economies of scale and rapidly rising Rx budgets



Source: Catenion

At the same time, a new biopharma S-curve slowly started to emerge in the late 1970‘s (mainly in the US) and is currently accelerating



Source: Catenion

In the proposed framework, the current - and anticipated future - acceleration of bio-pharmaceutical innovation is based on a number of factors working in conjunction…

- Huge investments in target discovery and validation
- Initially fuelled by the rise of genomics
- Increasingly multi-target treatment approaches

Drug format
Increasing choice of different formats

- Different anti-body formats
- siRNA, gene therapy, cell-based therapies, therapeutic vaccination, oligonucleotids, etc

Molecular Target
Increasingly starting point

New Drug

Target Population

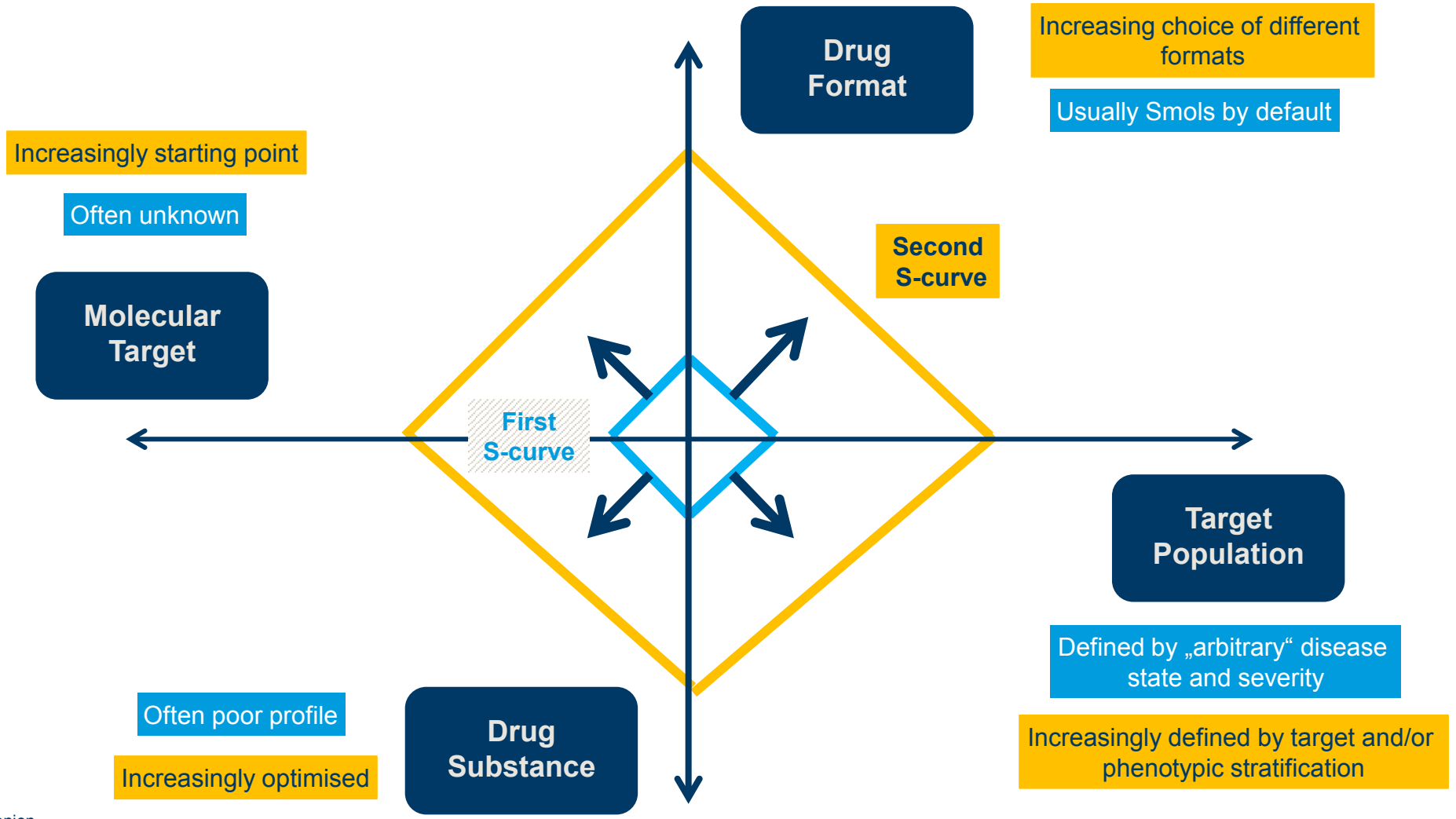
- Increasingly defined by target
- (biologics) and/or relying on phenotypic stratification

Drug Substance
Increasingly optimised

- Structure-based approaches
- Better screening techniques
- Better pre-clincial models
- Tox, PK, PD simulations
- etc

Source: Catenion

…taken together, these enabling technological changes considerably widen the scope for breakthrough innovation over and above that represented by the first S-curve…



Source: Catenion

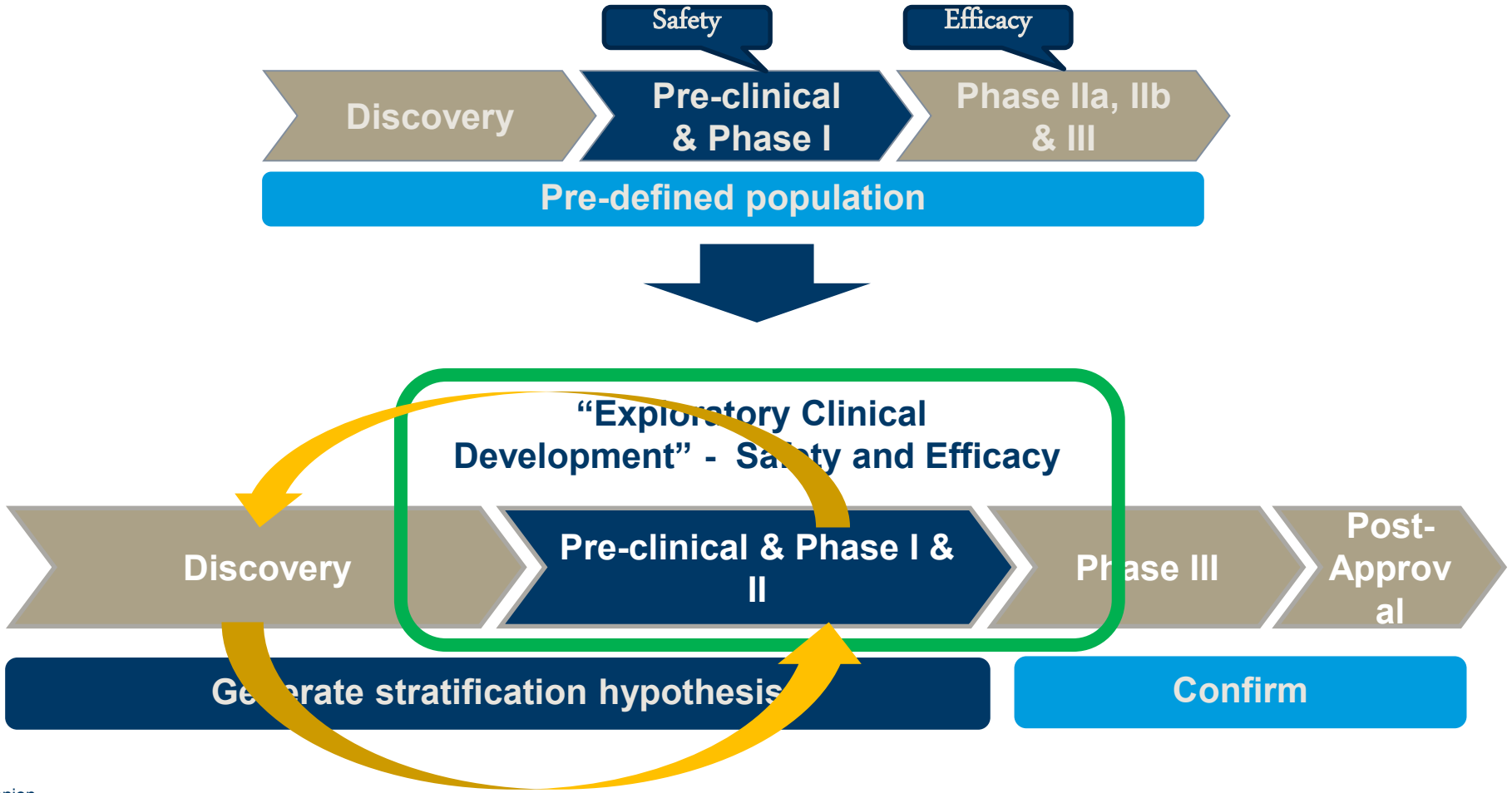
Redefining disease states constitutes a novel dimension of biomedical innovation – table after Prof Sir John Bell

Disease Taxonomy	
Symptom-based	Irritable Bowel Syndrome, Fibromyalgia
Histology	Angioimmunoblastic Lymphadenopathy
Physiology	Hypertension, Diabetes
Eponymous	Alzheimer‘s Disease, Bell‘s Palsy
Organ-based	Breast Cancer, Ovarian Cancer
End-of-the-Road	Heart Failure, Liver Failure

e.g.: Neo-glucogenesis by the liver vs dysregulated fatty acid metabolism, etc

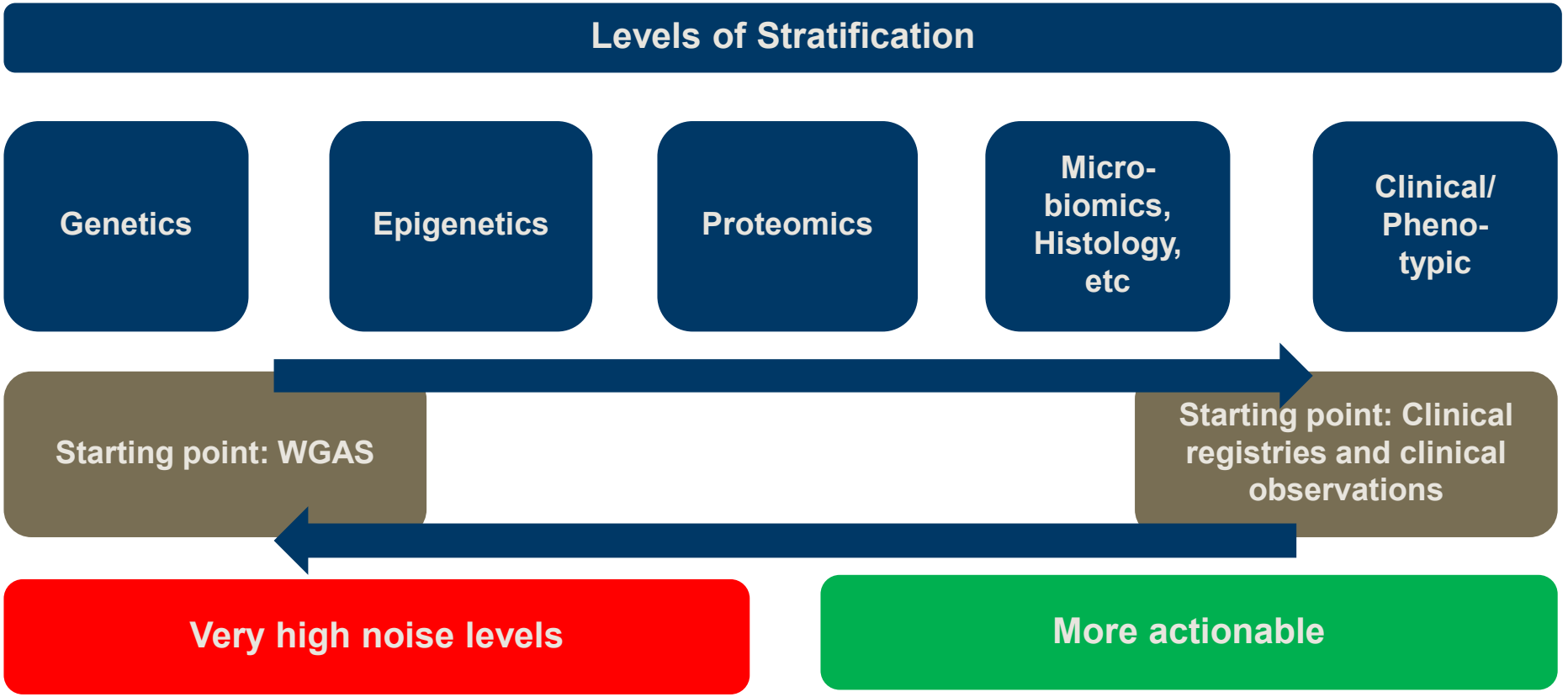
Source: Prof Sir John Bell https://www.youtube.com/watch?v=GBiYP6Pxvy0

In this environment, exploratory clinical development takes center stage, implying a massive need for collaborative TRANSLATIONAL RESEARCH of basic and clinical scientists



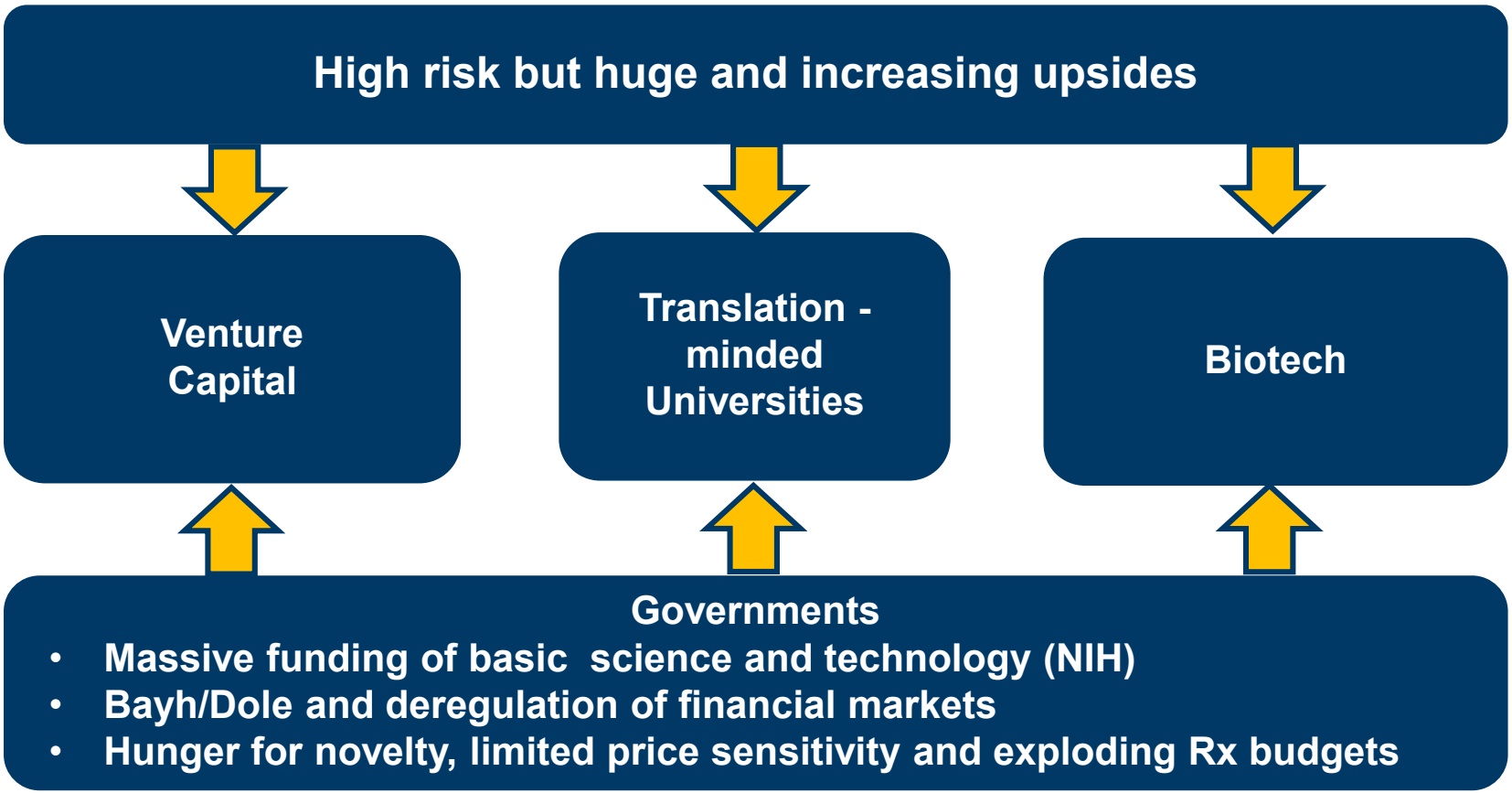
Source: Catenion

For many drug development projects, the likelihood of success will increase the more stratified the population is for which it is tested



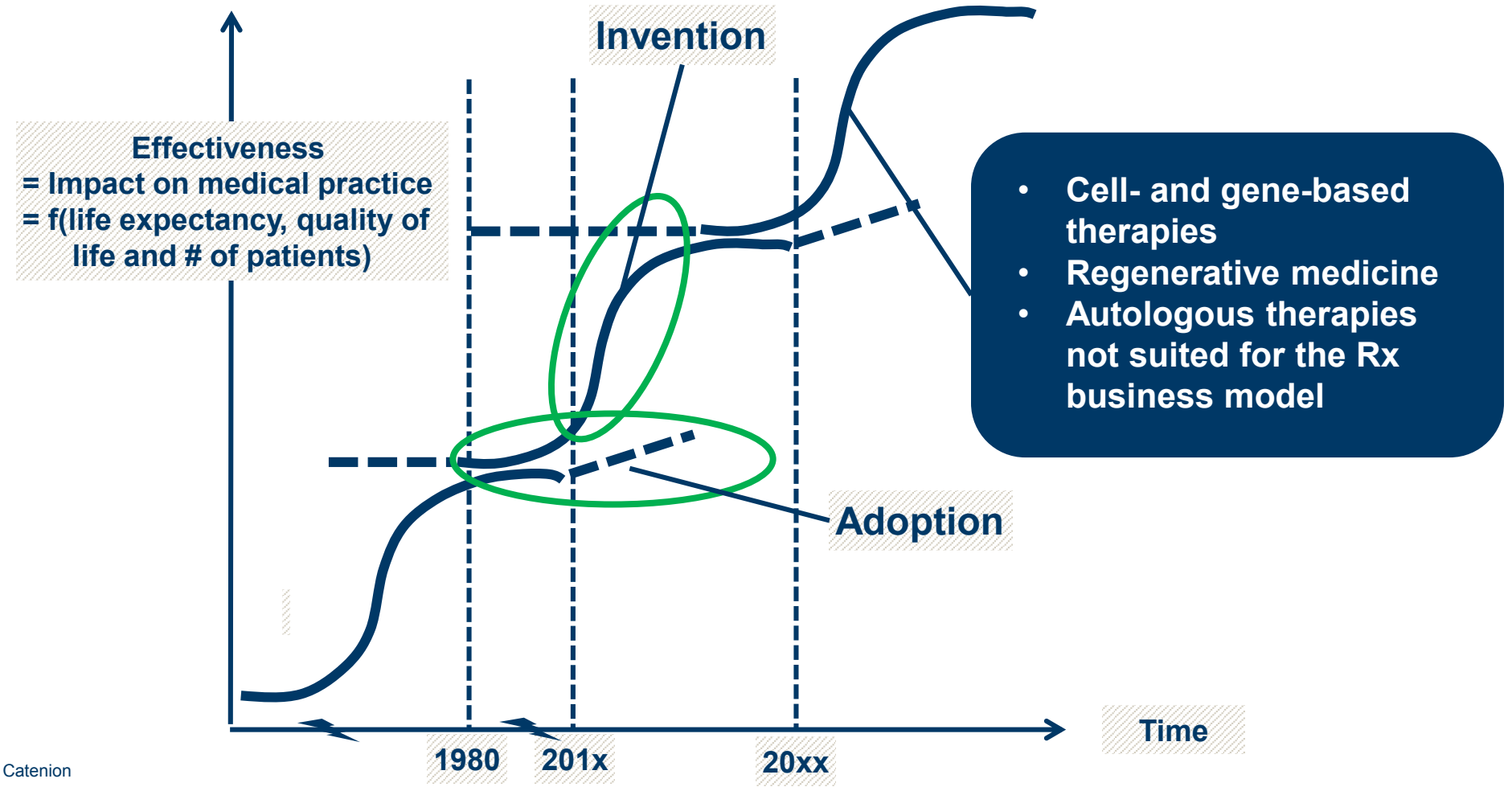
Source: Catenion

Emerging players on the second biopharma S-curve from 1980 onwards – universities, Biotechs and VCs, driven by deregulation, science focus, risk and increasing upsides; of course now joined by Pharma big and small..



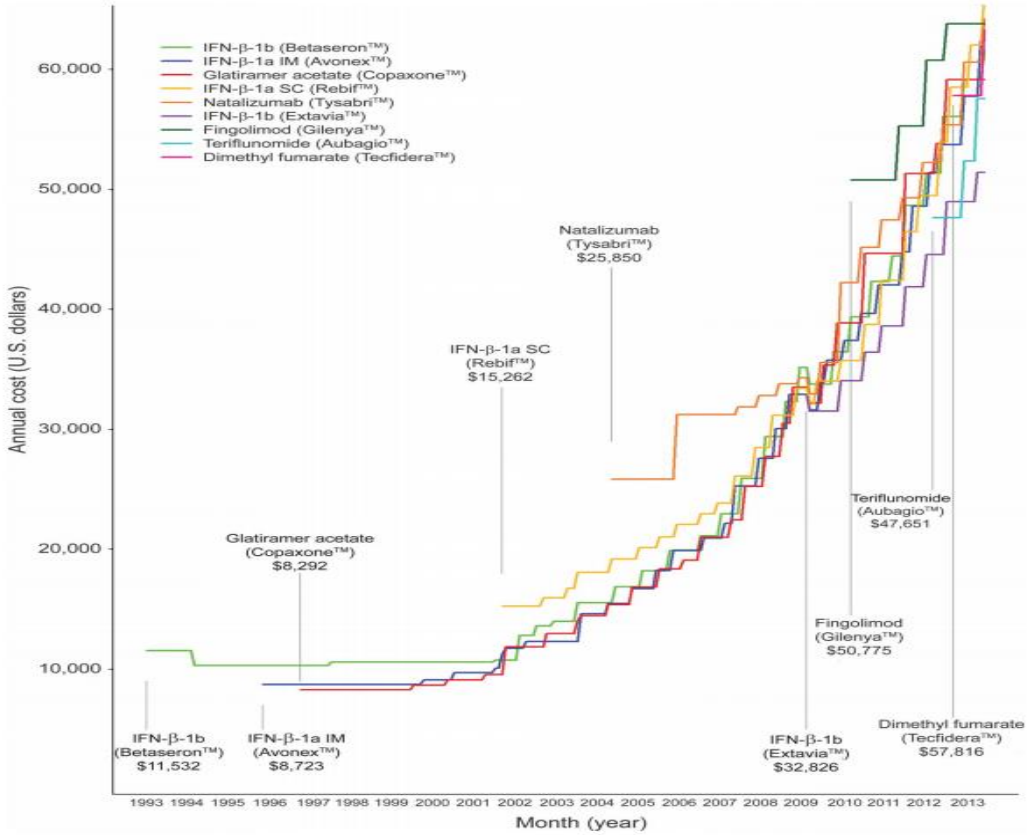
Source: Catenion

So now we have three innovation cycles running in parallel with unprecedented innovation potential combining invention with adoption, but in an unsustainable funding model



Source: Catenion

Especially on the second and now the third S-curve, price levels have continued to move - up leading to pushback from payors, limitations of access and ultimately raising the question of sustainability of the current model



Annual costs estimated from average wholesale prices (AWP), or wholesale acquisition costs if AWP not reported, and discounted 12%. IFN = interferon.

US list prices of MS drugs up more than six-fold since early 2000‘s

Source: Source: Hartung et al., 2015 Neurology

Agenda

- What is Biopharma Innovation and What Are We Measuring?
- Biopharma Innovation Cycles
- **Changing Roles of Different Players in Translational Research and Innovation**
- Brief Summary

Translational Research is not everything but it will be increasingly crucial to biomedical innovation

Disease biology

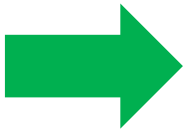
plus

Exploratory clinical research

New targets, modalities and drugs

plus

New definitions of disease states



Translational Research = Collaborative efforts between academia, university hospitals and industry

Source: Catenion

Advances in science and technology as well as economic pressures are changing the role of biopharma in biopharmaceutical innovation

R&D productivity crisis in Pharma

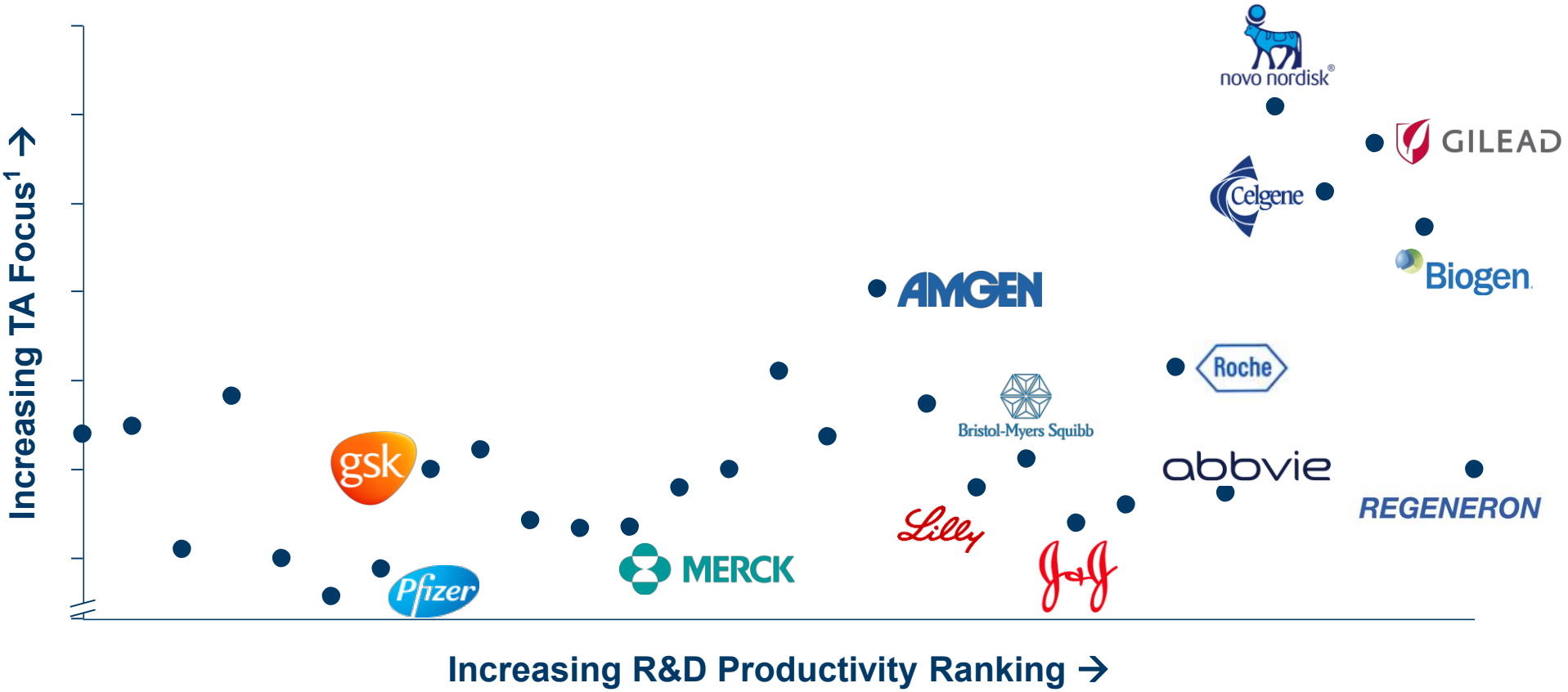
- Scaling back of in-house discovery in favour of „open innovation“ approaches
- Long-term industry/academia research alliances for specific fields
- Investment by pharma earlier in the value chain
- Increasing pressure by payors for highly clinically-differentiated drugs in the place of „just novelty“ as the basis for premium pricing

Emerging drug formats which Pharma does not know how to deal with

- Most new drug formats beyond small molecules originate in universities and require CMC know-how for development
- This know-how is typically generated by a new breed of CROs, not by pharma
- Autologous gene cum cell therapies do not fit the traditional pharma business model

Source: Catenion

Mid-sized companies with strong therapeutic focus show the highest R&D productivity



Source: Catenion Analysis, 1) % of Assets in Largest Two Therapeutic Areas

In the last decade, many universities have started translational initiatives to take advantage of the changing innovation dynamics

Mostly triggered and supported by national or regional government initiatives..

- E.g.: approx 30 CTSA grants from NIH (Harvard, NYU, Kansas, Iowa…) – total of $500mn
- Sweden, Flanders, Bioregions in Germany, Alberta, Wales...

..and/or embedded in strong biomedical innovation ecosystems

- E.g.: Boston, South san Francisco, Golden Triangle, Flanders, Bio-regions in Germany...

What will drive success in the Translational Research required to leverage scientific potential into medical interventions?

Source: Catenion

First of all, the deep cultural divide between academia and industry needs to be tackled; this is rooted in values, lack of mutual understanding and (often) arrogance

Culture

Academia

- Scientific excellence
- Curiosity & Creativity
- Academic freedom
- Focus on publications

- Poor replicability
- Poor project management
- Lack of discipline

Industry

- Commercial Success
- Focus on IP
- R&D Productivity

- Little room for serendipity
- Constantly changing strategies and priorities
- Intransparent decision-making

Source: Catenion

Translation by definition cuts across domains, so it is not surprising that some of the key cultural divides are to be found INSIDE each of the players

Culture

Source: Catenion

Universities should combine academic values with professional project management - the world will be poorer if universities become profit-driven enterprises – example SPARK Stanford

Culture

Collaborative, bottom-up initiative initiated and driven by a protein chemist and a clinician

Focus on education and mentoring of PIs for selected high-impact projects

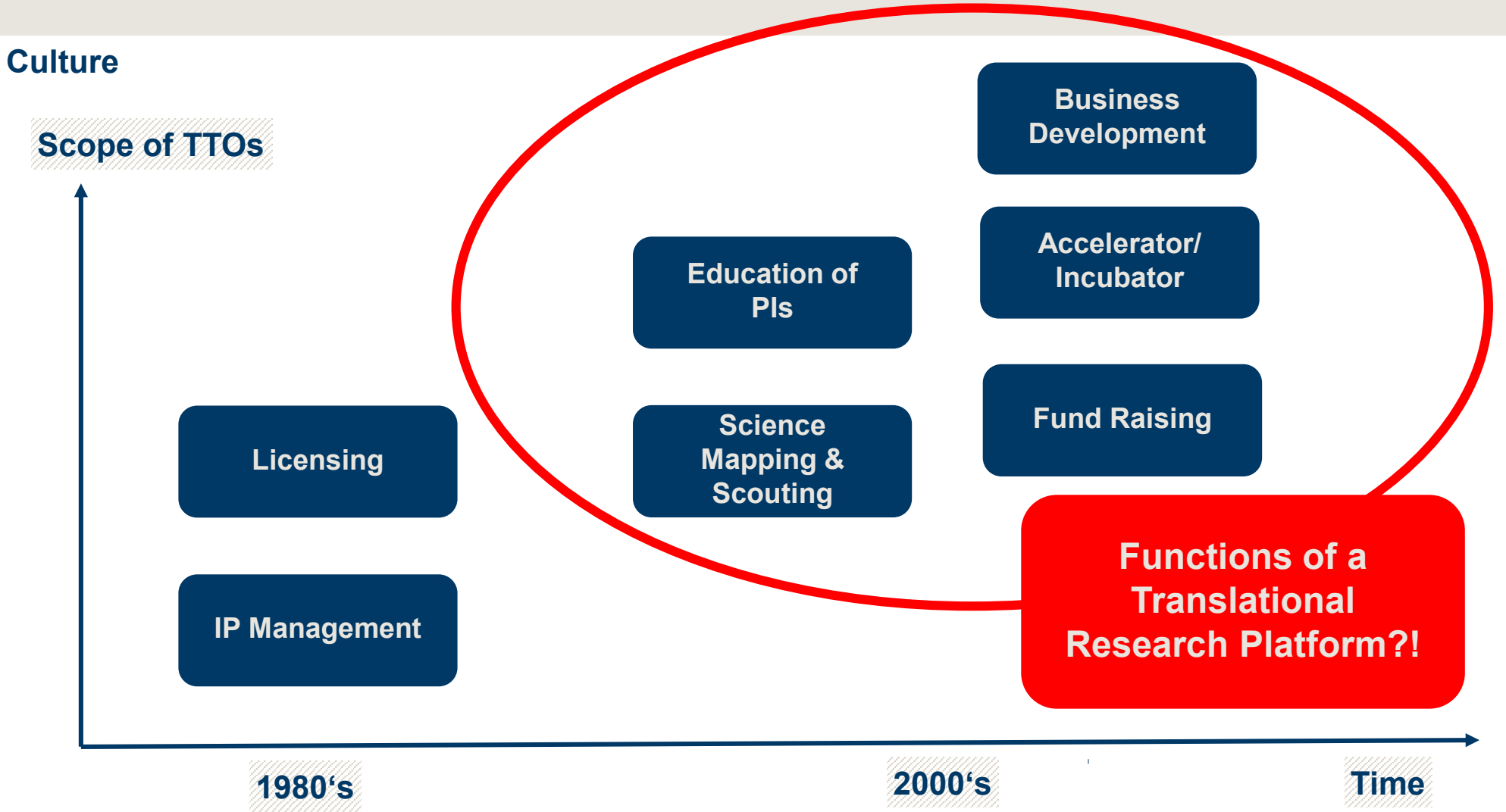
Virtual organisation domiciled within the Stanford School of Medicine

Strong Set of Values

- **Academic freedom, scientific excellence and potential clinical impact**
- **Commercial potential is just one criterion**
- **Culture of open discussion and challenging regardless of hierarchy („check your ego at the door“)**
- **Voluntary contribution of time and advice by scores of pharma advisors**
- **No agreements with pharma in search of financial return**

Source: SPARK, Catenion, more detailed information is available from Catenion

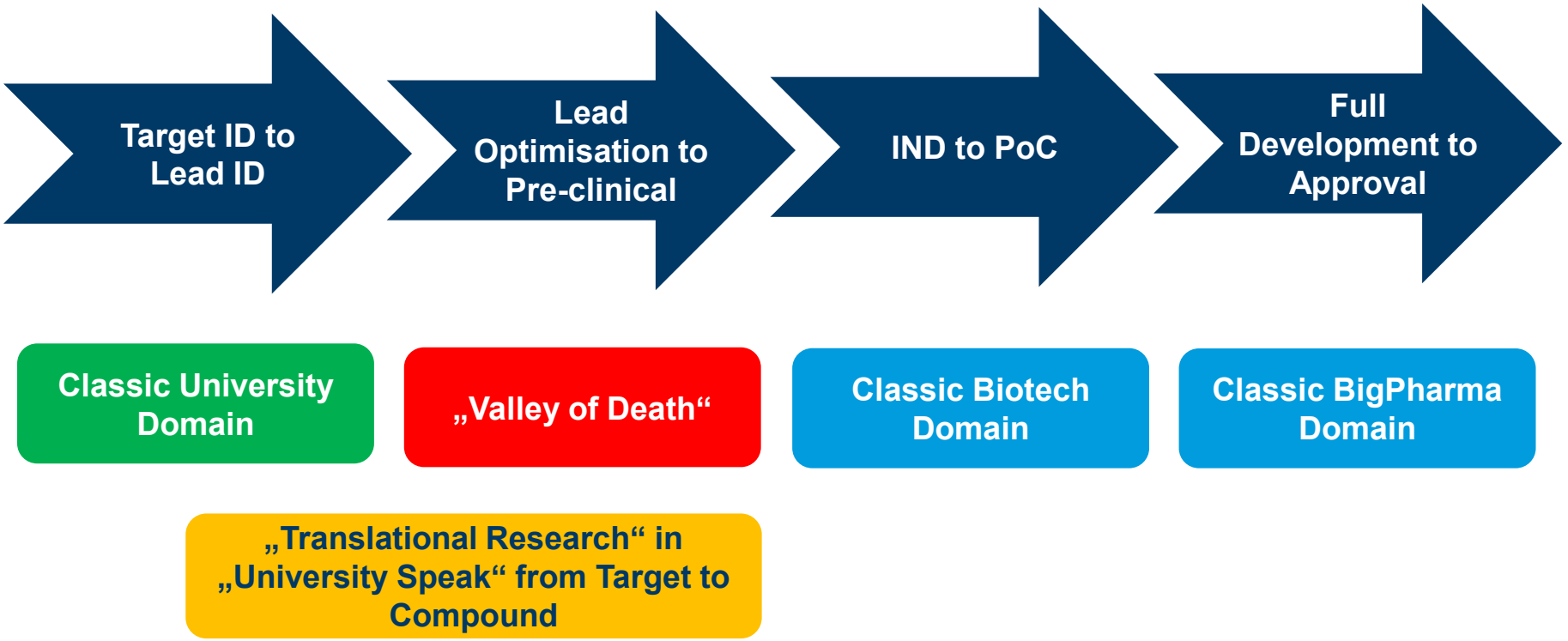
Due to the historical development of TTOs and Translational Research, there are additional fault lines inside universities



Source: Catenion

„Translational Research“ in traditional university speak aims at bridging the „Valley of Death“ in order to generate IP that can be licensed or spun off into a start-up company („from target to candidate“)

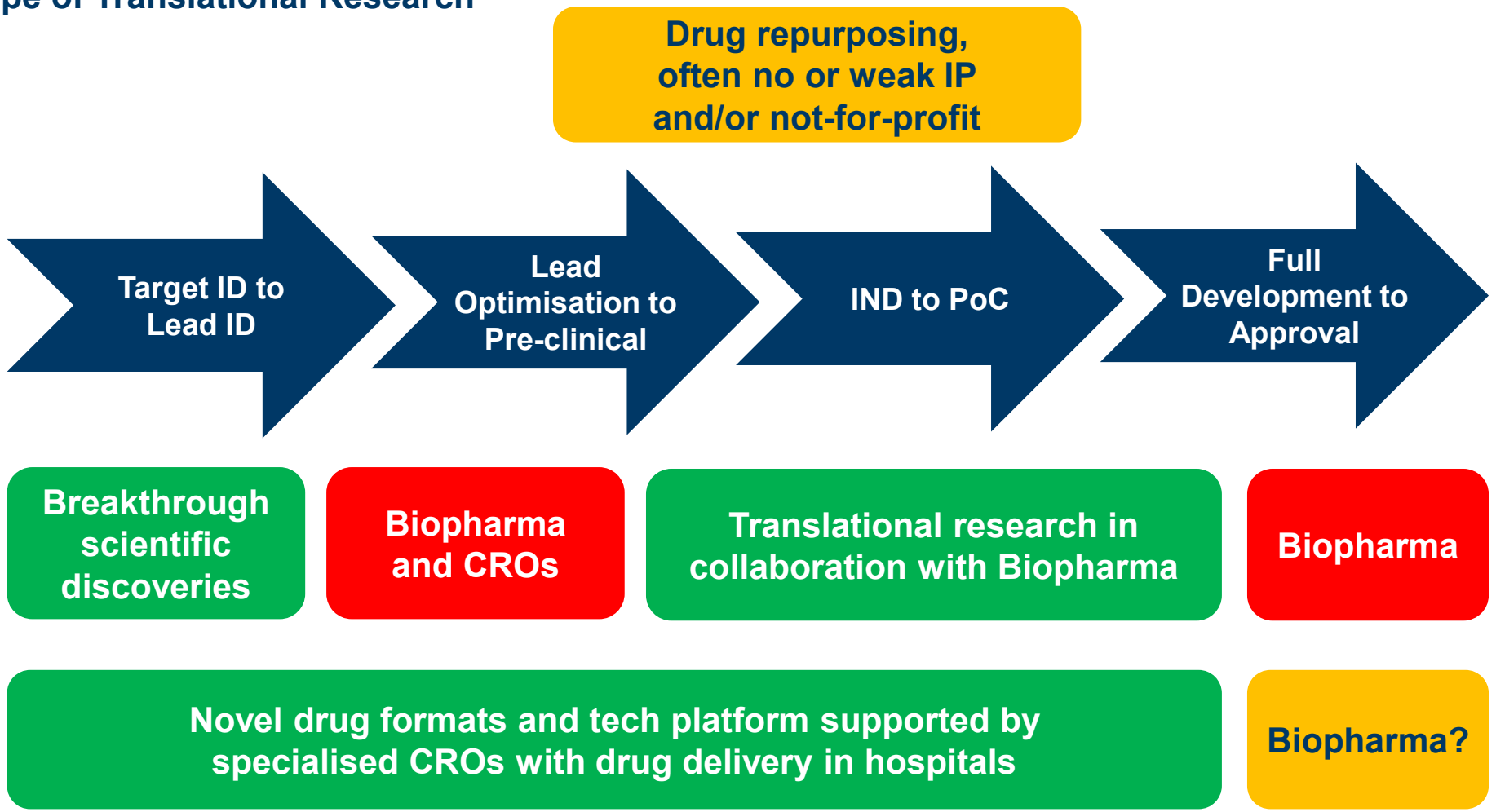
Scope of Translational Research



Source: Catenion

So where can universities play in the emerging environment? A priori, the scope is large if the work is carried out according to the professional standards of industry required to get drugs to market…

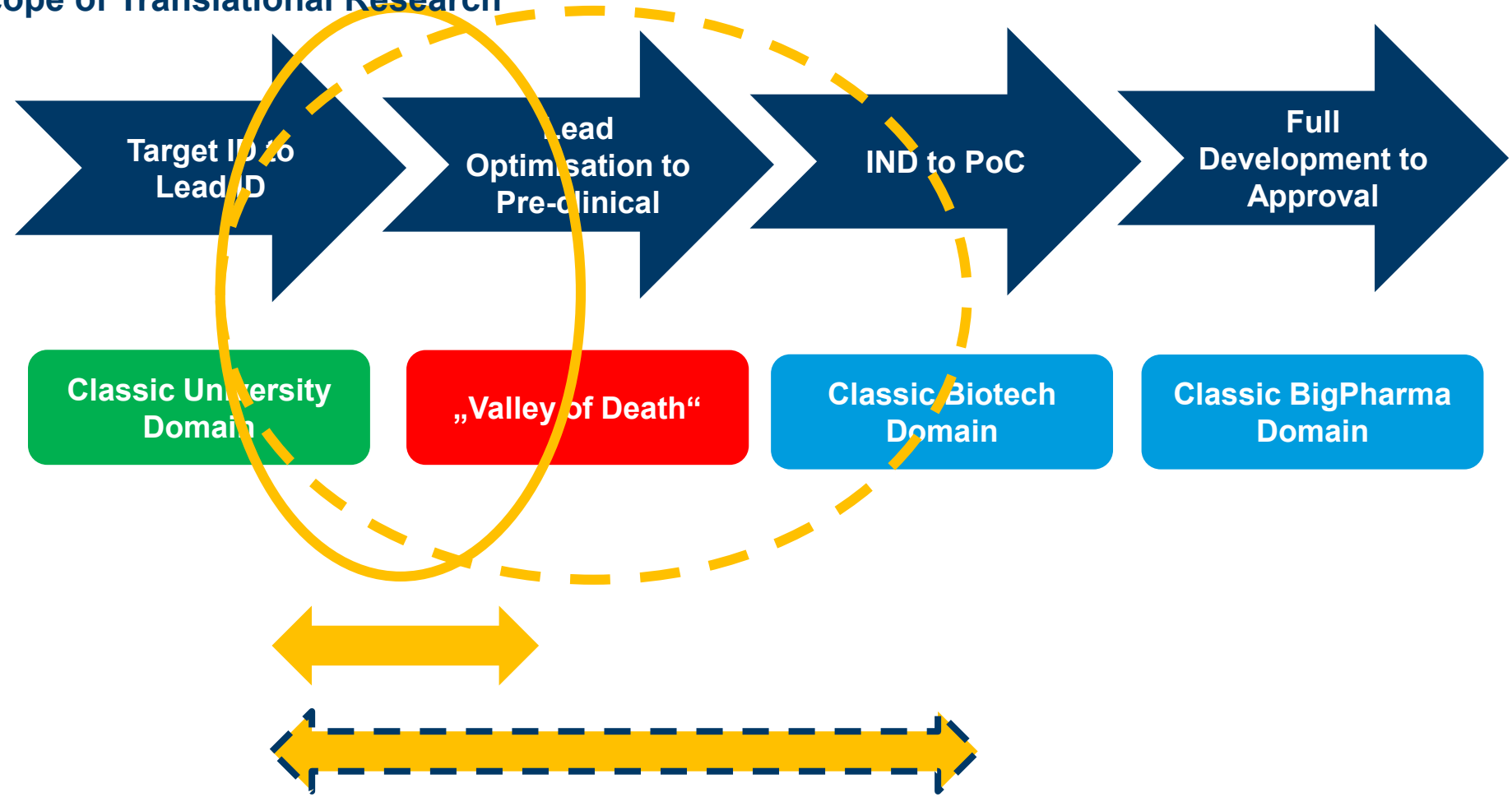
Scope of Translational Research



Source: Catenion

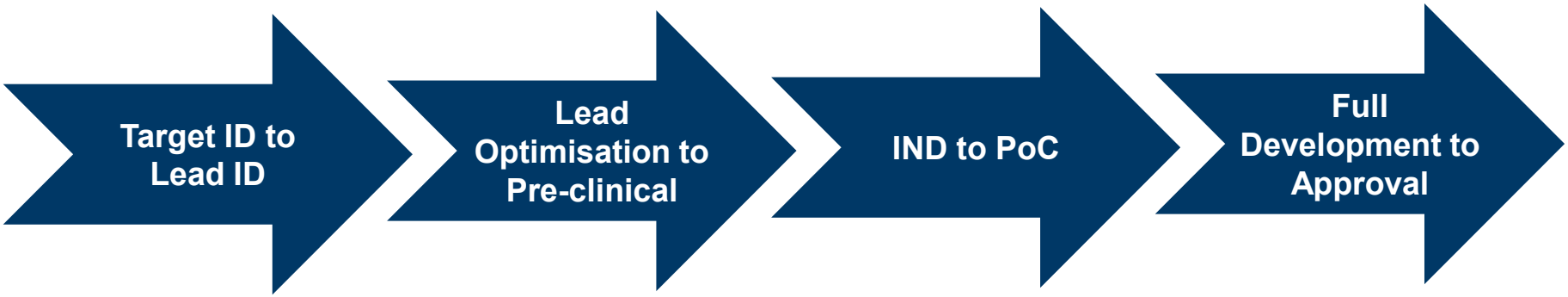
In any event, in order to build a competitive position in Translational Research, the focus of universities needs to expand forward into the early clinic („from bench to bedside“)

Scope of Translational Research



Source: Catenion

…but as the cost escalates once projects move into the clinic, this strategy requires either collaborative approaches with pharma or a different funding model (e.g.: CTSA grants)



Investigator grants

New grant instruments

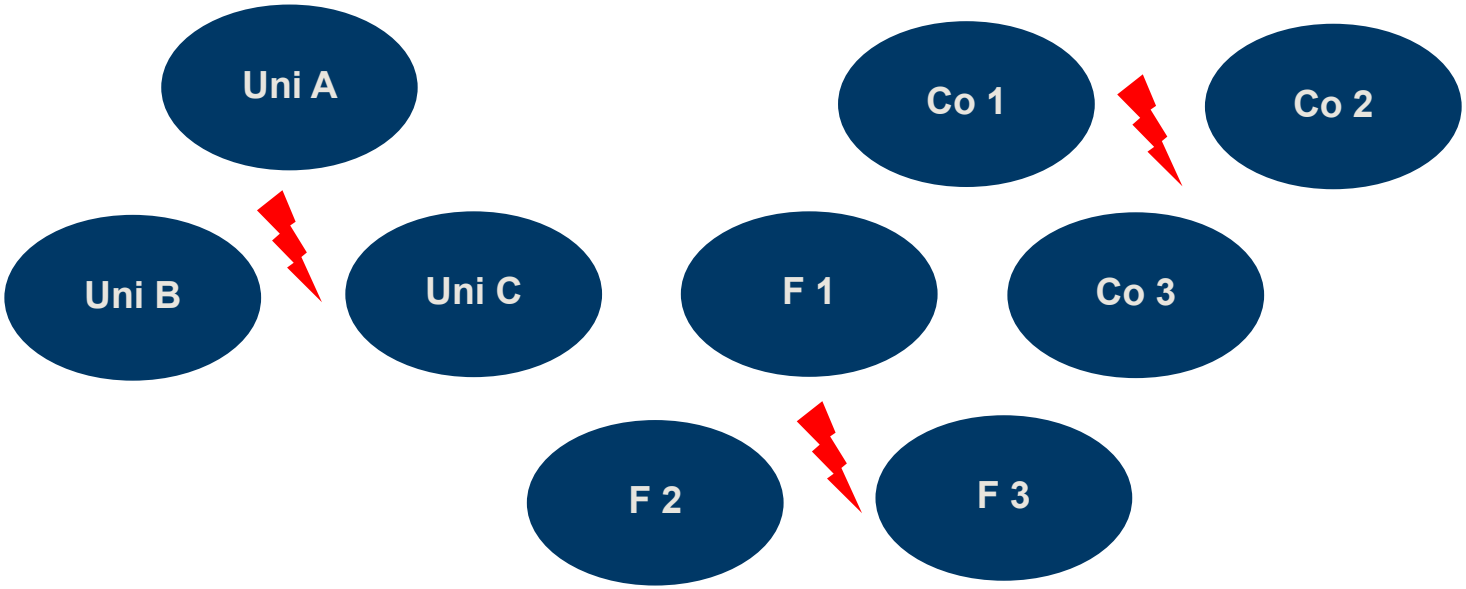
Biopharma only

Collaboration between academia and biopharma

Source: Catenion; CTSA = Clinical and Translational Science Awards, granted by NCATS, the NIH National Center for Advancing Translational Sciences

Universities and other biomedical players are often engaged in heated local competition....

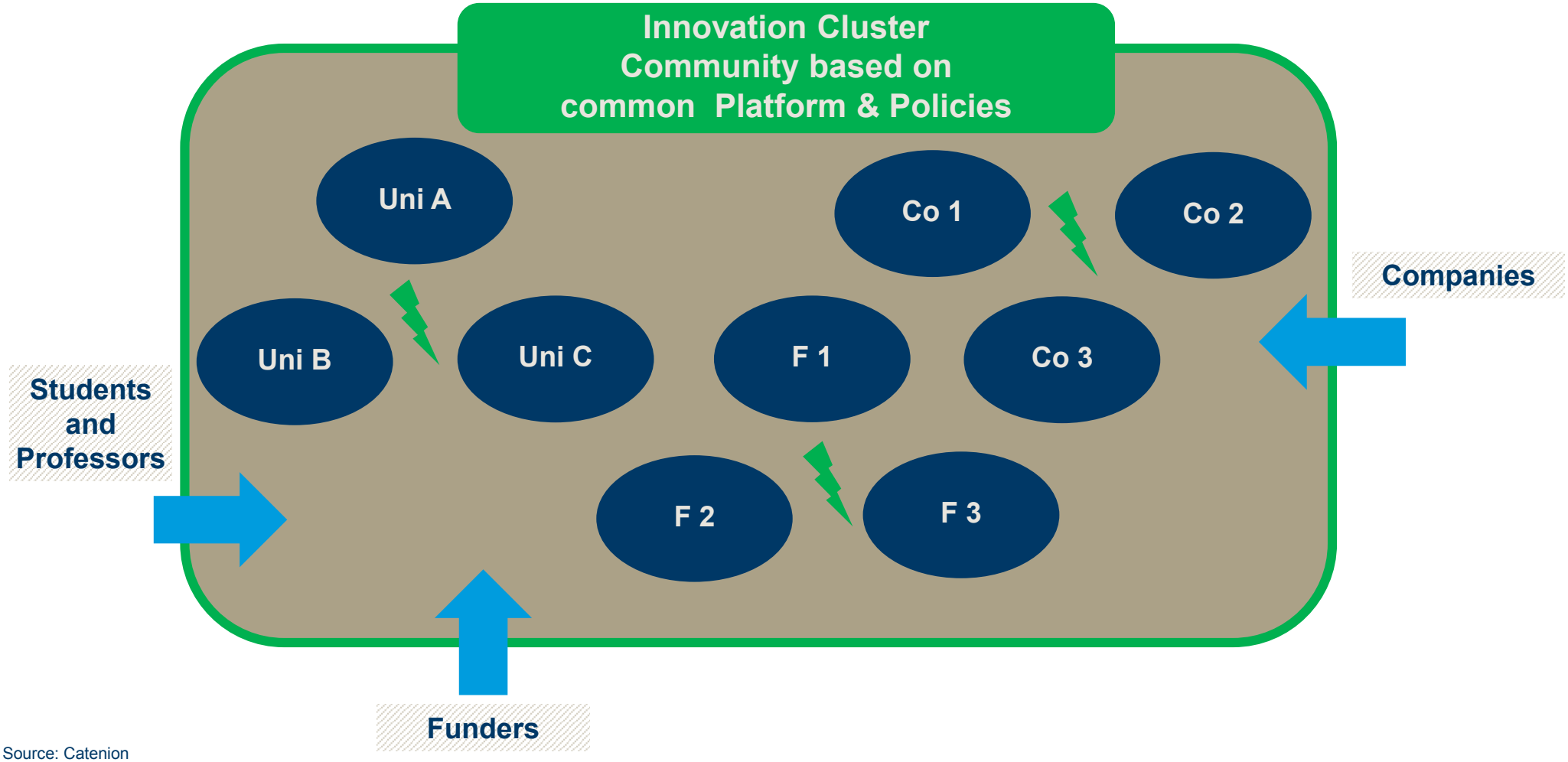
Getting on the Map



Source: Catenion

...forming a biomedical innovation cluster will attract third parties and make all participants stronger in global competition (which is the one that really counts)

Getting on the Map



Source: Catenion

As biopharma and VCs are chasing good ideas in academia, collaboration models are evolving rapidly into more strategic/long-term set-ups, increasingly reaching into the clinic

Historic model: small annual grants to basic researchers

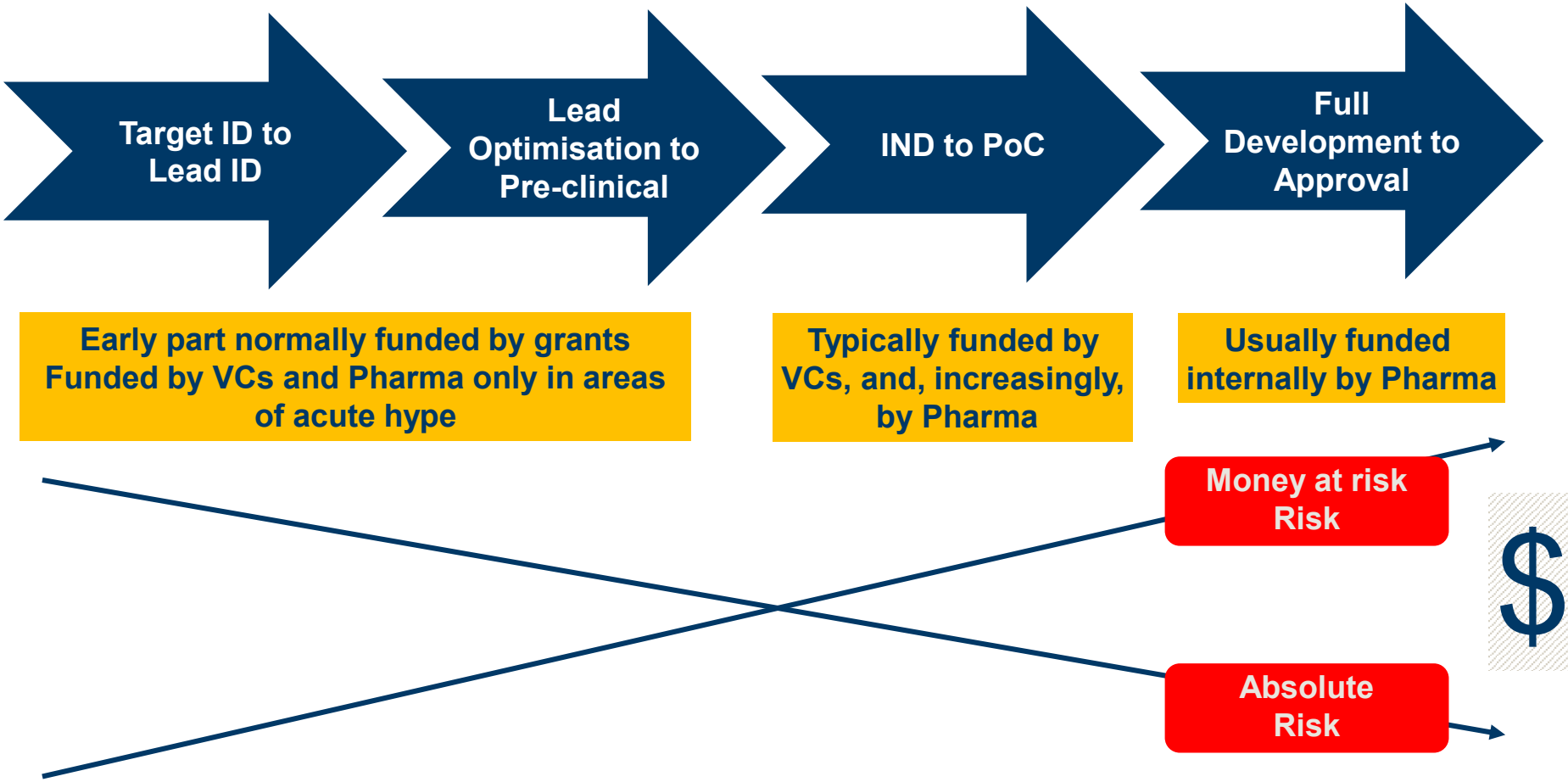
- **Takeda/Flagship/New York Tri**
- **Versant/Inception/Rx/academia**

- **German Centre for Neurodegenerative diseases/Orion**

Source: Catenion

Historic funding models have used a high proportion of private „**money at risk**“ to finance biomedical innovation – **this needs to be compensated by high returns and puts sustainability at risk**

Funding Models



Source: Catenion

If we want lower prices, we need to rely less on private risk money – is Telethon Italia (originators of the SCID therapy) a model for things to come?

Funding Models

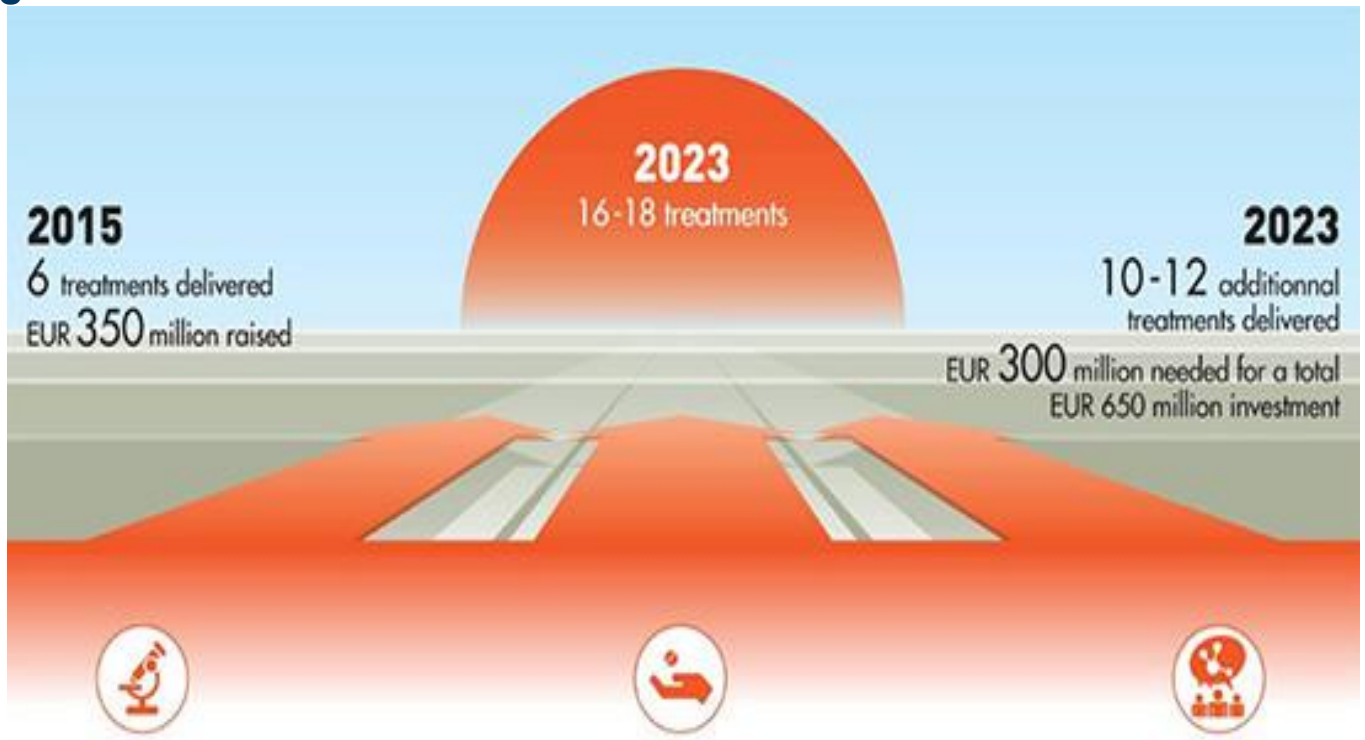
Fondazione Telethon Italia

Scientific Excellence	Charity Funding	Professional management	Industrial Partnerships
Telethon scientific publications 1991-2014: 10.222 articles in peer-reviewed journals Impact second only to MRC	€45mn in grant volume pa 2/3 intra-mural research, 1/3 to single researchers in Italy	First research lab to receive GLP certification for gene and cell therapy toxicity and bio-distribution studies	Collaborating with GSK, Biogen, Shire, Biomarin

Source: Telethon Italia

Another potential model of things to come: DNDi – Drugs for Neglected Disease initiative – why only for neglected diseases?

Funding Models



- **Not for profit virtual model**
- **Numerous co-operations with biopharma and CROs**
- **Funding from private donors and public agencies**
- **Attrition-adjusted cost of NCE $110-170mn (estimate)**

Source: DNDi – Drugs for Neglected Disease initiative

Agenda

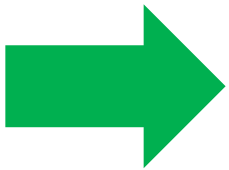
- What is Biopharma Innovation and What Are We Measuring?
- Biopharma Innovation Cycles
- Changing Roles of Different Players in Translational Research and Innovation
- **Brief Summary**

In the future, policy-makers will hold the keys to unlocking innovation potential based on translational research at affordable prices

- Support the creation of clusters to attract scientists and companies from everywhere to drive excellence

- Increase the amounts of grant funding for translational projects including in the early clinic

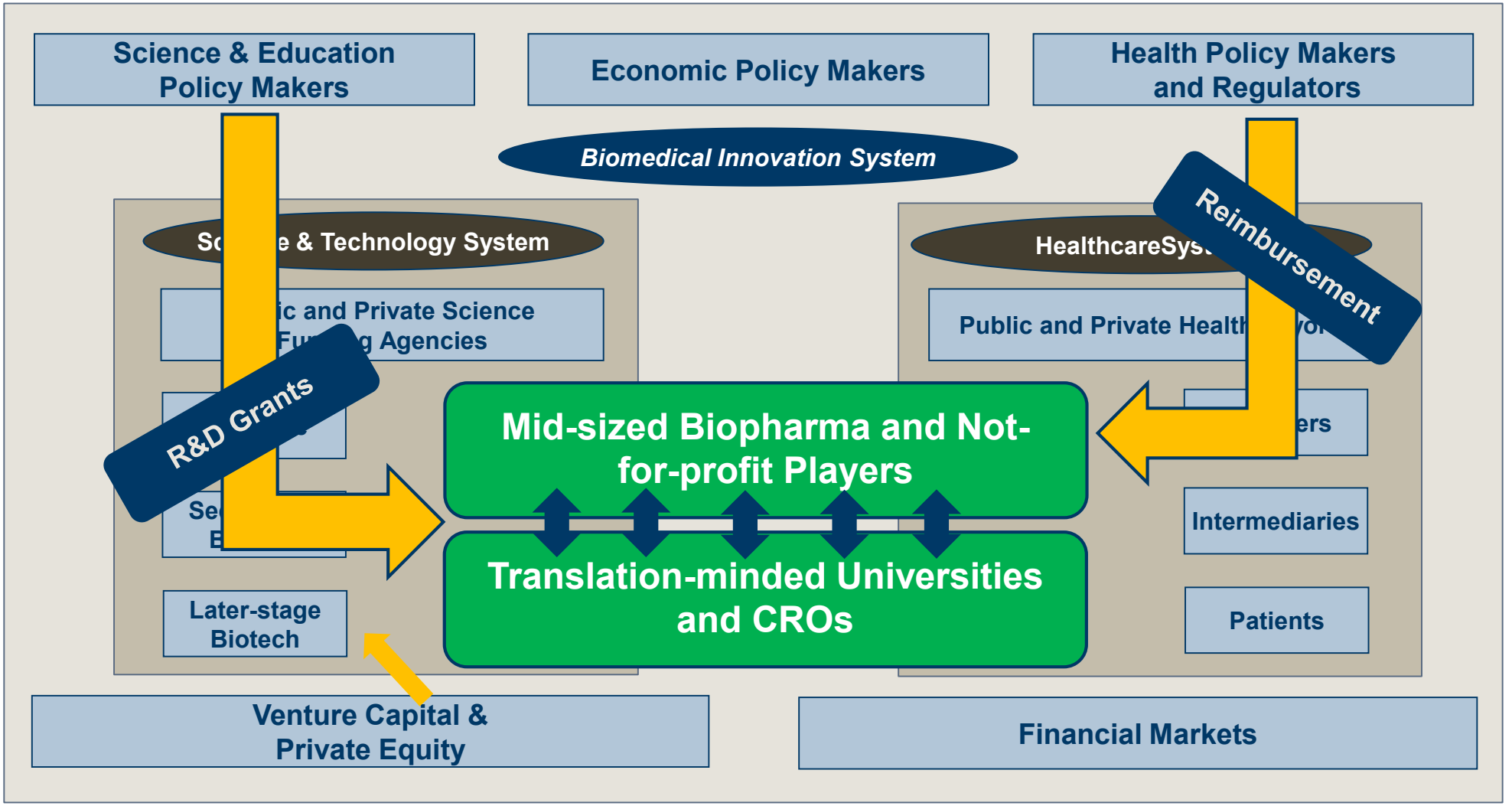
- Gradually reduce price levels as more grant-funded drugs come on stream



- Move from R&D funding by rewarding past success to funding based on the merits of current projects

Source: Catenion

If R&D funding gradually shifts from high reimbursement levels to direct R&D grants, universities, mid-sized biopharma and not-for-profit players stand to play a larger role, especially if integrated into regional innovation clusters



Source: Catenion

To finish, three burning questions for you to think about

Why is Tokyo not one of the leading global hubs for biomedical innovation ?

What does it take to get there?

Are more Japanese Big Pharmas, VCs and start-ups really the answer?

Source: Catenion

Contact

Berlin

Hausvogteiplatz 12
10117 Berlin
Germany

phone : +49 30 20 63 99 60
email: berlin@catenion.com

London

180 Piccadilly
London W1J 9HF
United Kingdom

phone: +44 207 917 9511
email: london@catenion.com

New York

405 Lexington Avenue
Chrysler Building, 26th Floor
New York, NY 10174
United States

phone: +1 212 203 7276
email: newyork@catenion.com

Tokyo

Marunouchi Trust Tower L20
1-8-3 Marunouchi, Chiyoda-ku
Tokyo 100-0005
Japan

phone: +81 3 5288 5270
email: tokyo@catenion.com

www.catenion.com

Source: Catenion