IMPORTANCE OF NEW COMPANIES FOR INNOVATION

Presentation for the symposium on
Capitalism, Entrepreneurship, and Sustainability
In conjunction with the Farewell Lecture of
Prof. Dr. Ben Dankbaar

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Part 1: Advantage new companies

Analysis of the origins of all 252 new drugs approved by FDA 1998-2007

Source: Kneller. 2010. Nature Reviews Drug Discovery 9

COLOR KEY

Discovery* in biotechs (new companies formed after 1975) or in universities followed by biotechs undertaking initial development, **B + U>B**. E.g: bevacizumab (Avastin, Genentech) & zanamivir (Relenza, Monash U > Biota), bortezomib (Velcade. ProScript), aglasidase (Fabrazyme, U Michigan > Coulter)

Discovery* in universities, and first development undertaken by a biotech in a different geographic region, **U>Bout**. E.g: adefovir (Hepsera) & tenofovir (Viread) (Czech Ac Sci & Catholic U Leuven > Gilead)

Discovery* in universities, and first development undertaken by a an established company (pharma), **U>P**. E.g: oxaliplatin (Eloxatin, Nagoya City U. > Tanaka Kikinzoku); cetuximab (Erbitux, UCSD & Weizmann Institute > Rorer)

Discovery* in a small established pharmaceutical company (all European, < 500 employees), **Ps**. E.g: , modafinil (Provigil, Lab. Lafon)

Discovery* in a large established pharmaceutical company, **P**. E.g: , pioglitazone (Actos, Takeda); capecitabine (Xeloda, Roche Japan)

*Discovery usually means discover of the active therapeutic compound.

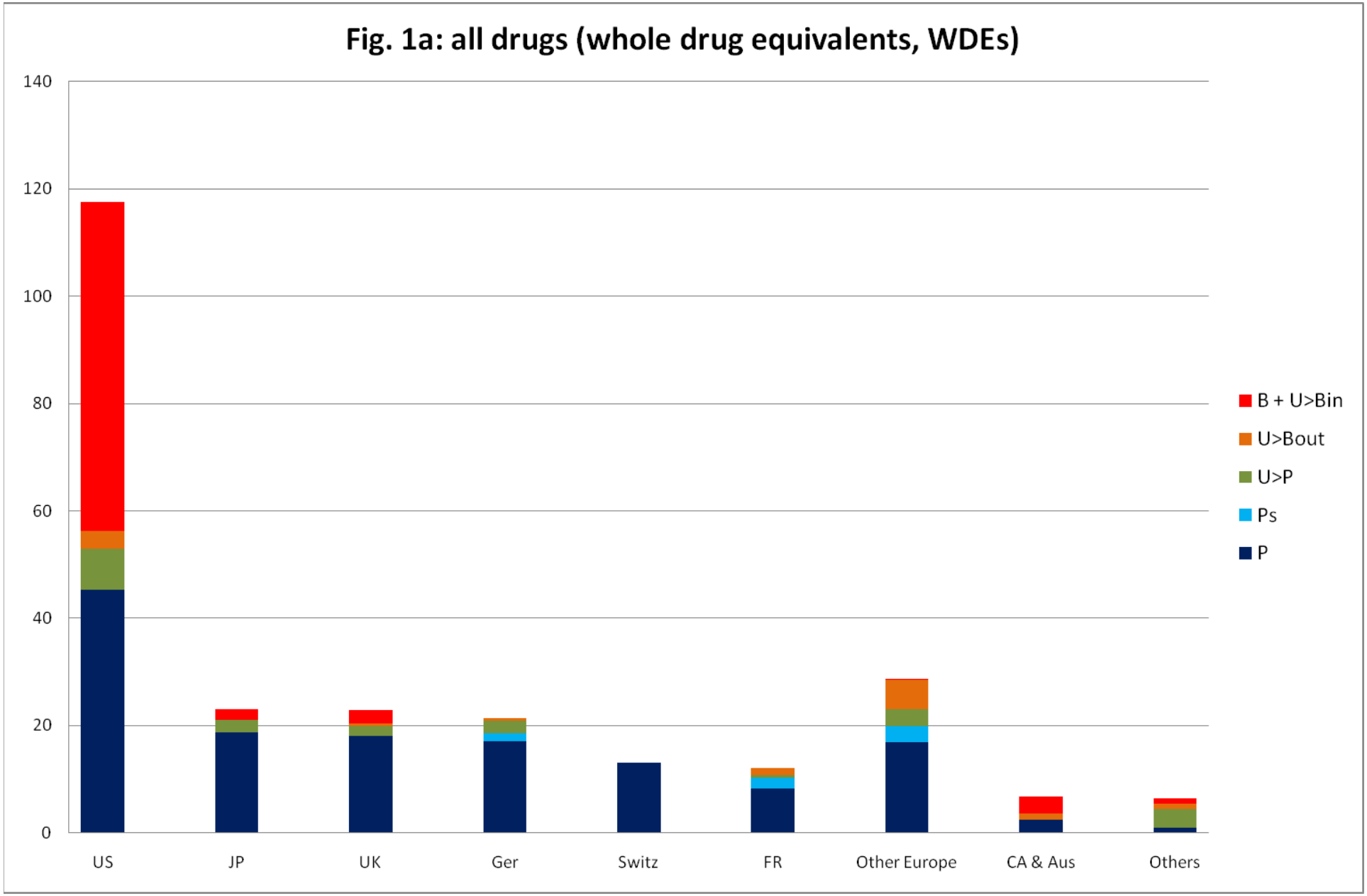


Fig. 1a: all drugs (whole drug equivalents, WDEs)
140
120
100
80
60
40
20
0
US
JP
UK
Ger
Switz
FR
Other Europe
CA & Aus
Others
B + U>Bin
U>Bout
U>P
Ps
P

All drugs classified according to innovativeness by two methods FDA (1998-2007)

1. Scientific novelty
2. Health benefit

1. Scientific novelty

Novel if either

(a) new mechanism of action

or

(b) first in a distinct class of compounds

If marketed within 3 years of first-marketed drug in Japan, Europe or US, still qualifies as novel.

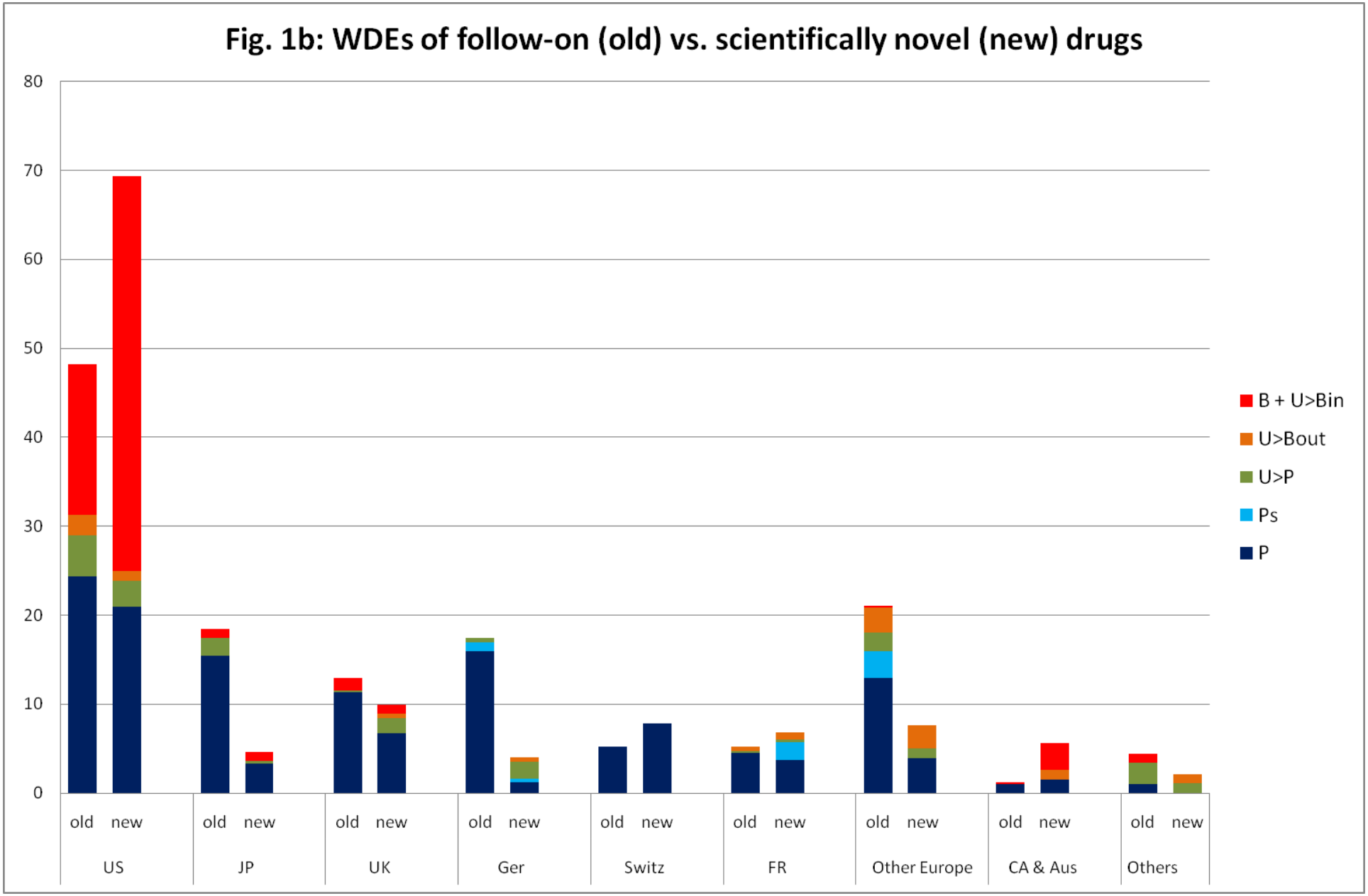


Fig. 1b: WDEs of follow-on (old) vs. scientifically novel (new) drugs
80
70
60
50
40
30
20
10
0
old new
US
old new
JP
old new
UK
old new
Ger
old new
Switz
old new
FR
old new
Other Europe
old new
CA & Aus
old new
Others
B + U>Bin
U>Bout
U>P
Ps
P

2. Health benefit

Classification relies on whether FDA granted *priority* or *standard* review of New Drug Applications (NDAs) in the case of new molecular entities (NMEs, small molecule drugs).

- *Priority review* (to be completed in < 6 months) for drugs that offer "substantial benefit over currently marketed therapeutics" (designated by **p** in charts).
- *Standard review* (in principle, < 12 months) for other NMEs (designated by **s** in charts).
- Drugs reviewed under Biologic License Applications (BLAs) were analyzed separately, because before 2004, priority or standard review status was often not recorded for biologics (designated as **b** in charts). Biologics analyzed separately as one group.

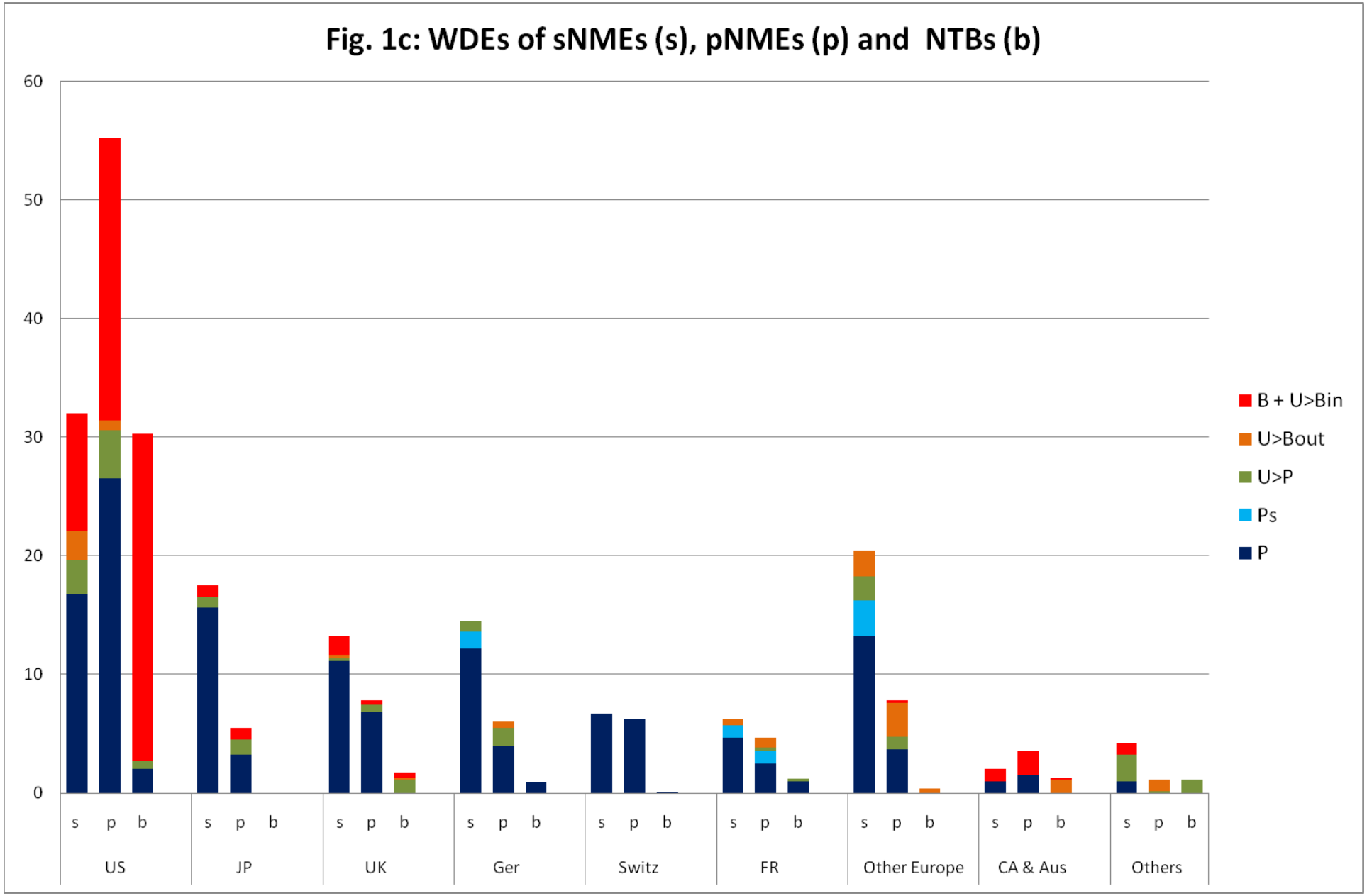


Fig. 1c: WDEs of sNMEs (s), pNMEs (p) and NTBs (b)
60
50
40
30
20
10
0
s p b
US
JP
UK
Ger
Switz
FR
Other Europe
CA & Aus
Others
B + U>Bin
U>Bout
U>P
Ps
P

Same patterns even if classify on basis of peak world wide sales rather than number of drugs

- However, biologics account for the high peak sales of biotech and university > biotech drugs.
- Sales of university > biotech small molecule drugs tend to be low. (Many are orphan drugs.)

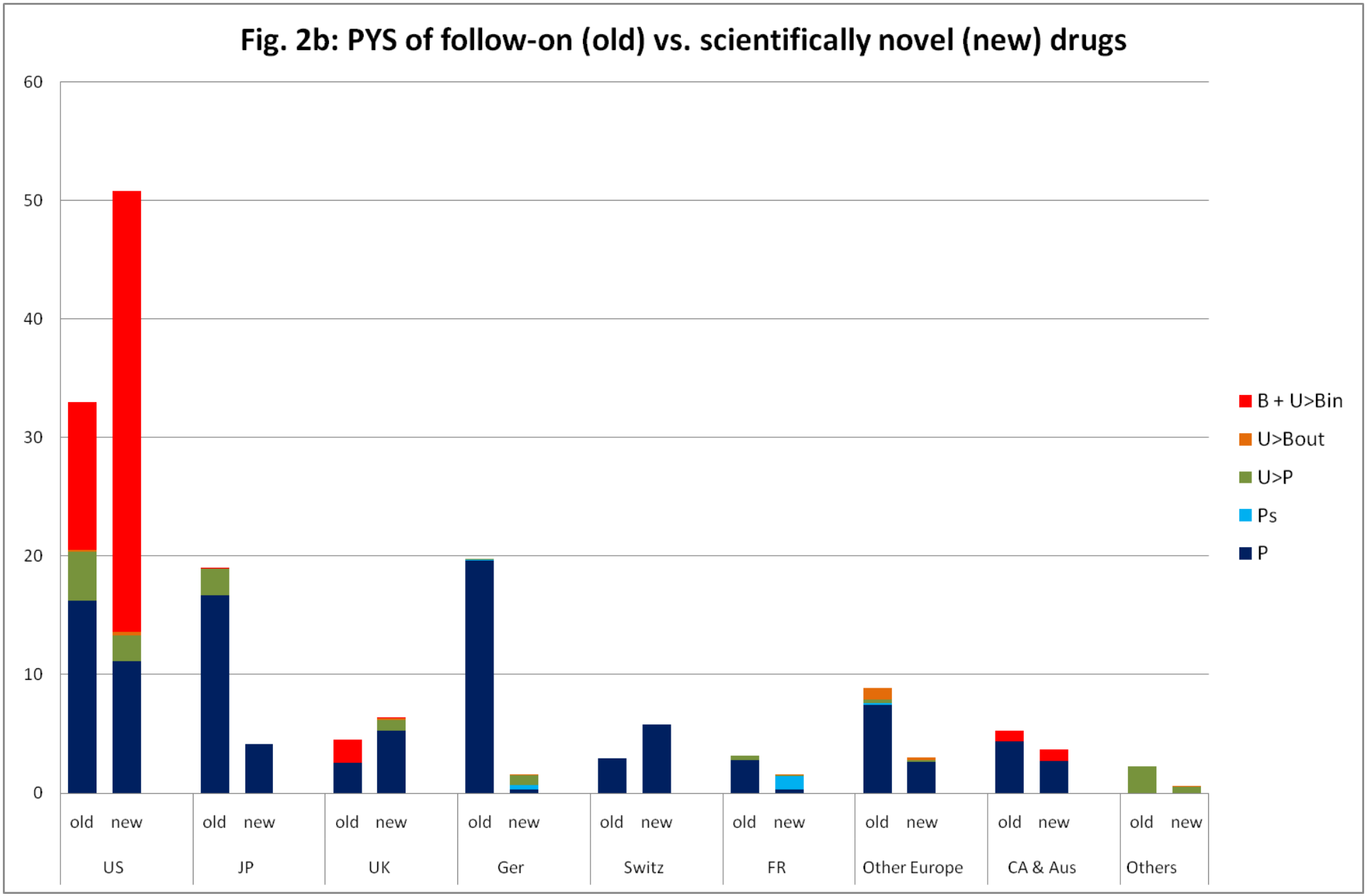


Fig. 2b: PYS of follow-on (old) vs. scientifically novel (new) drugs
60
50
40
30
20
10
0
old new
US
old new
JP
old new
UK
old new
Ger
old new
Switz
old new
FR
old new
Other Europe
old new
CA & Aus
old new
Others
B + U>Bin
U>Bout
U>P
Ps
P

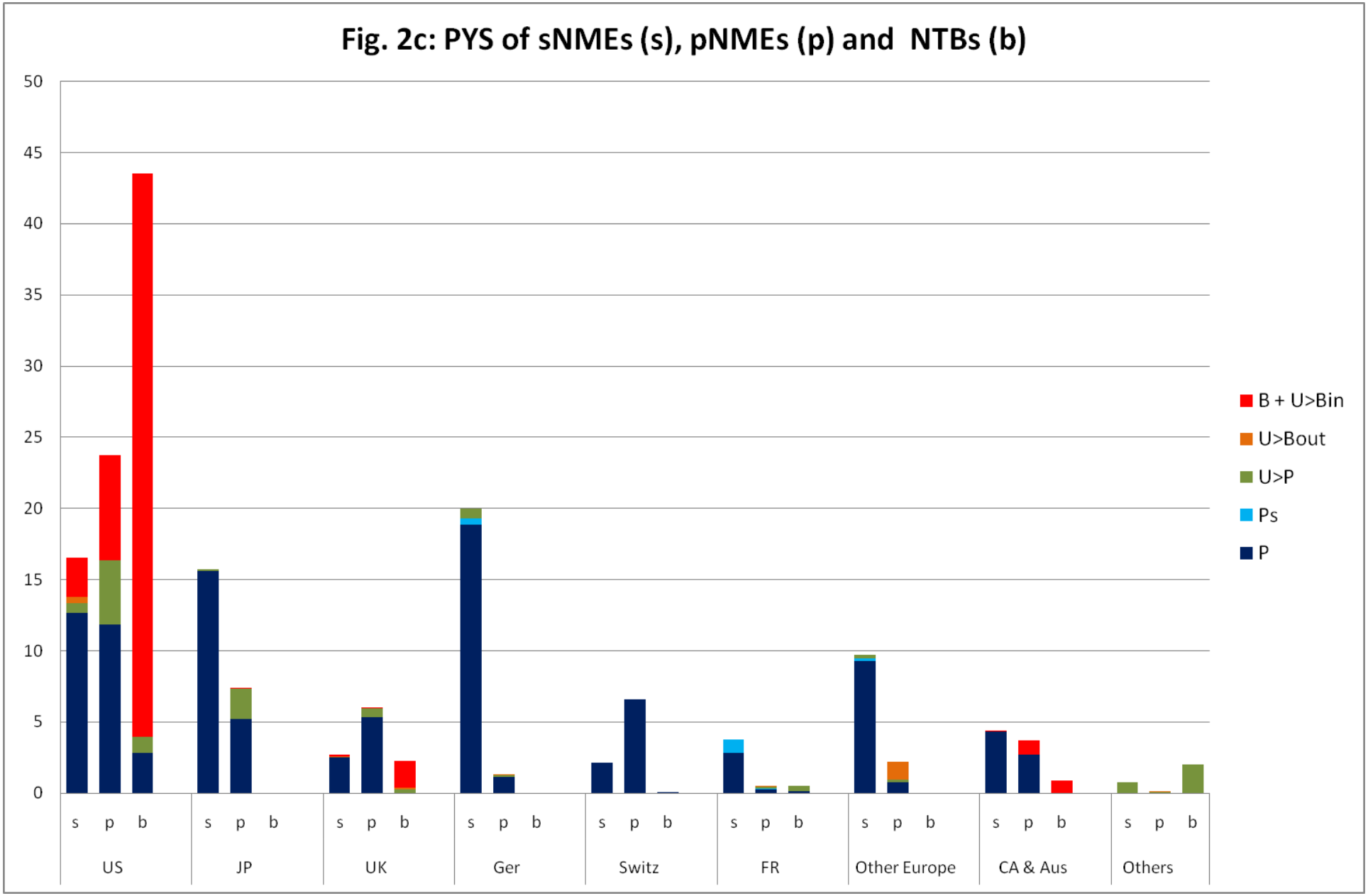


Fig. 2c: PYS of sNMEs (s), pNMEs (p) and NTBs (b)
50
45
40
35
30
25
20
15
10
5
0
s p b
US
JP
UK
Ger
Switz
FR
Other Europe
CA & Aus
Others
B + U>Bin
U>Bout
U>P
Ps
P

Startups are especially suited to carry out initial development of university discoveries.

- Hardly any innovative drugs discovered in universities anywhere in the world were initially developed by major pharmaceutical companies.
- Overall, startups are much more likely to discover innovative drugs or to undertake the initial development of innovative university drugs, than are established companies.

Other fields where new companies have been innovation leaders

- Biomedical devices
- Robotic surgery
- Gene sequencers
- 3D printers
- Internet communications & social media

Fields where they are among the leaders

- Semiconductor manufacturing equipment
- High efficiency solar cells & other clean tech
- MEMS sensors

Fields that they pioneered historically

- Semiconductors and switchers
- Hard disk drives

Implications

- New companies have an advantage in initiating and pushing forward early development of novel products
  - Provided the environment supports entrepreneurial companies

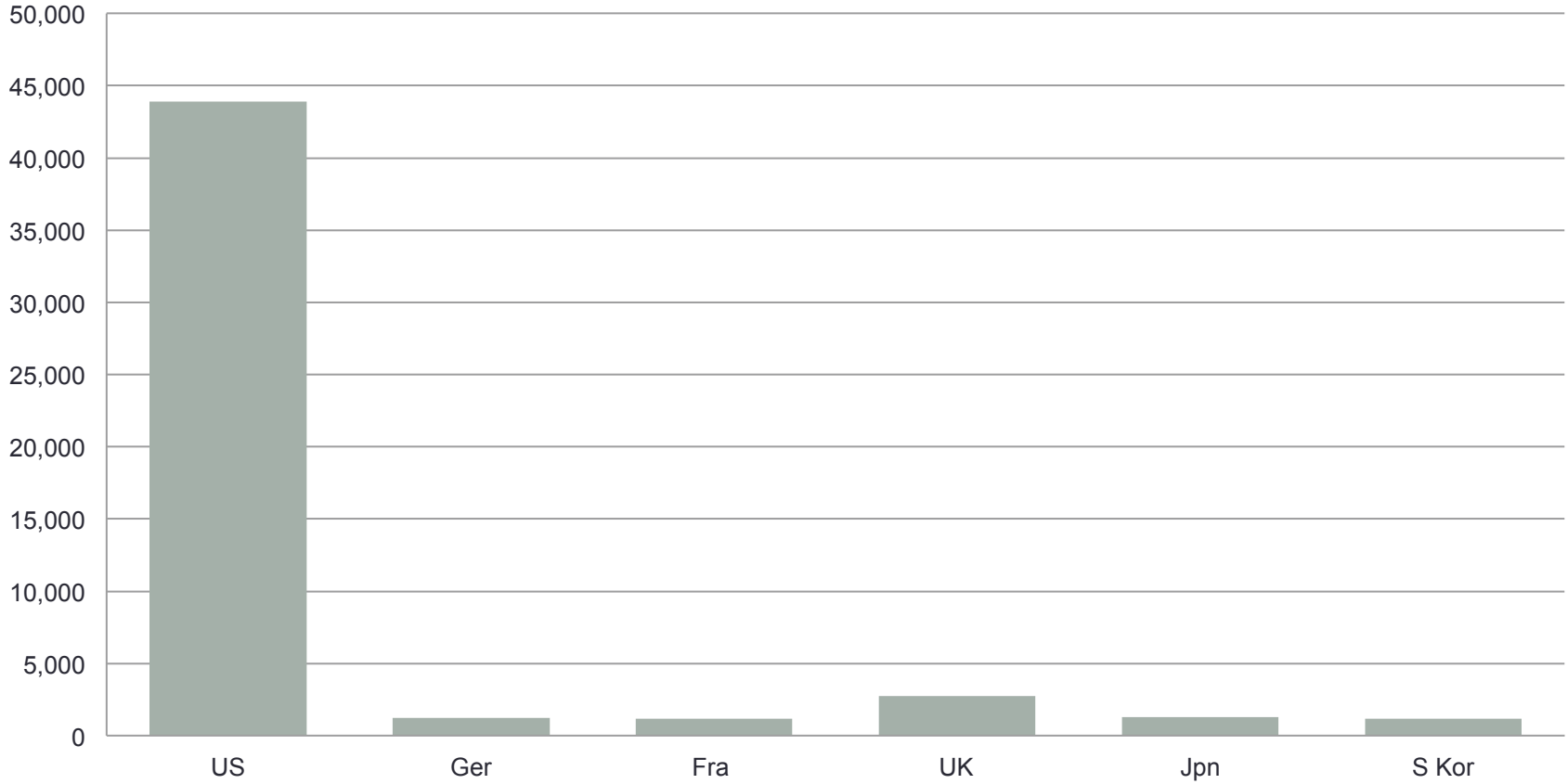
Rationale

- Large companies pre-occupied with major customers and products. (Christensen)
- Mobility of people and capital characterizes (and is a pre-condition for) a supportive start-up environment. Thus such an environment redistributes human and financial resources to areas where they are most productive.
  - Saxenian and Hyde extolling Silicon Valley (SV) style high velocity labor market
  - Also results in rapid knowledge exchange
- Japan's fundamental problem may be too many human and financial resources locked up in old organizations doing old things.

Part 2: Doubts and qualifications

Lots of government support behind success of US biotechs (but for basic research)

Government health R&D outlays 2009 (millions USD)
source: NSB, Science & Engineering Indicators 2012



Traditional venture capital (VC) funding model under great stress

Some would say “irreparably broken”

- VC and angel funding difficult to obtain in US, especially for pharmaceuticals
  - Siphoning off by IT and social media
  - VC funding for bio startups may be easier in Japan
- Often one hears “public support needed for startups”
  - Does not indicate system is healthy

Even if funding could be solved, is level of individual risk sustainable?

- Human cost in economic downturns
- Does SV model depend upon unsustainable high level of immigration or high young:elderly population ratio?
- Typical startup seeks to minimize employment

[But do tentative signs of return of manufacturing to America suggest system is self correcting?]

Maybe startups can be engines of innovation only in America

or in “Anglo Saxon” countries (excepting the UK?)

- Recalls “liberal” vs “coordinated” market economies from varieties of capitalism literature
  - Liberal market systems provide better environment for startups, coordinated markets more suitable for large companies
  - Radical innovation comes more naturally to startups, incremental innovation to large companies,
- Consistent with the drug origin data

Large companies have great capacity for innovation

- US pharmaceutical companies have discovered many innovative drugs in-house
  - Many in labs that have been closed, e.g.:
    - Pharmacia in Sweden
    - Wyeth in New York State
    - Sandwich in UK
    - Upjohn in Michigan

  All closed after mergers with Pfizer.

Additional examples of large company innovation

- Carbon fiber technology from Toray
- Safer and more fuel efficient cars (especially from German and Japanese auto makers)
- New innovative drugs from Genetech (a mature biotech)

Emergence of “new” innovation model

Large companies collaborating with universities

- German automakers with German and US universities
- Pfizer-UCSF, Glaxo Smith-Kline with various universities world wide
- Prevalent in Japan where it is easy for companies to control university intellectual property

Part 3: Rebuttal

What evidence that innovative, disruptive technologies will emerge from closer collaboration between universities and big companies?

Interviews with Japanese companies indicate they are not likely to develop novel disruptive technologies outside their main business focuses

- A few counter examples (exceptions that prove rule?):
  - Computer controlled industrial robots Fujitsu > Fanuc
  - Solar cells from Sharp

Examples of new, disruptive technologies developed by startups

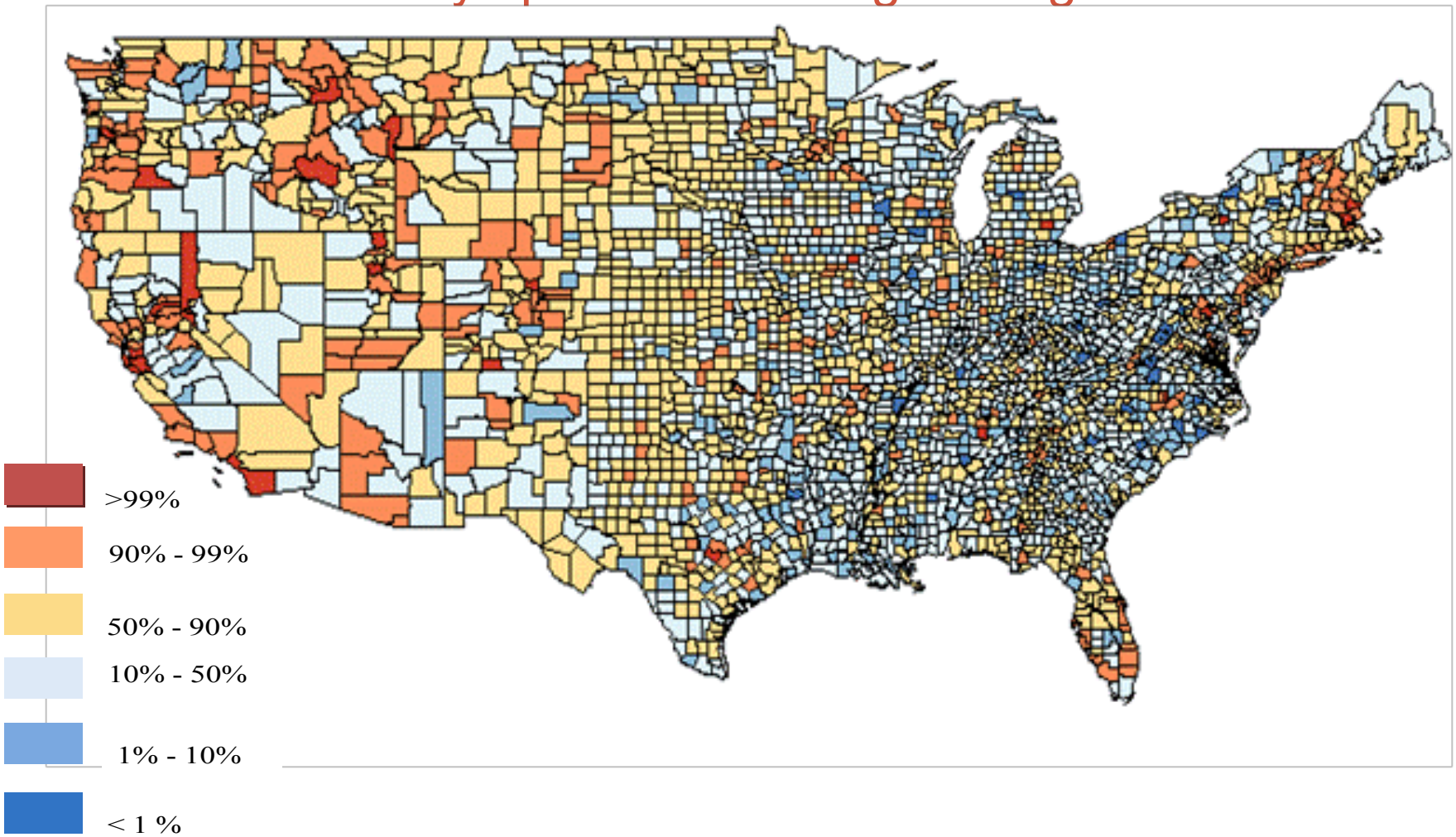
- Biologic drugs (e.g., therapeutic antibodies)
- The great IT technologies that came out of Bell Labs, PARC were developed by Intel and Apple

Fundamental problem with established company innovation

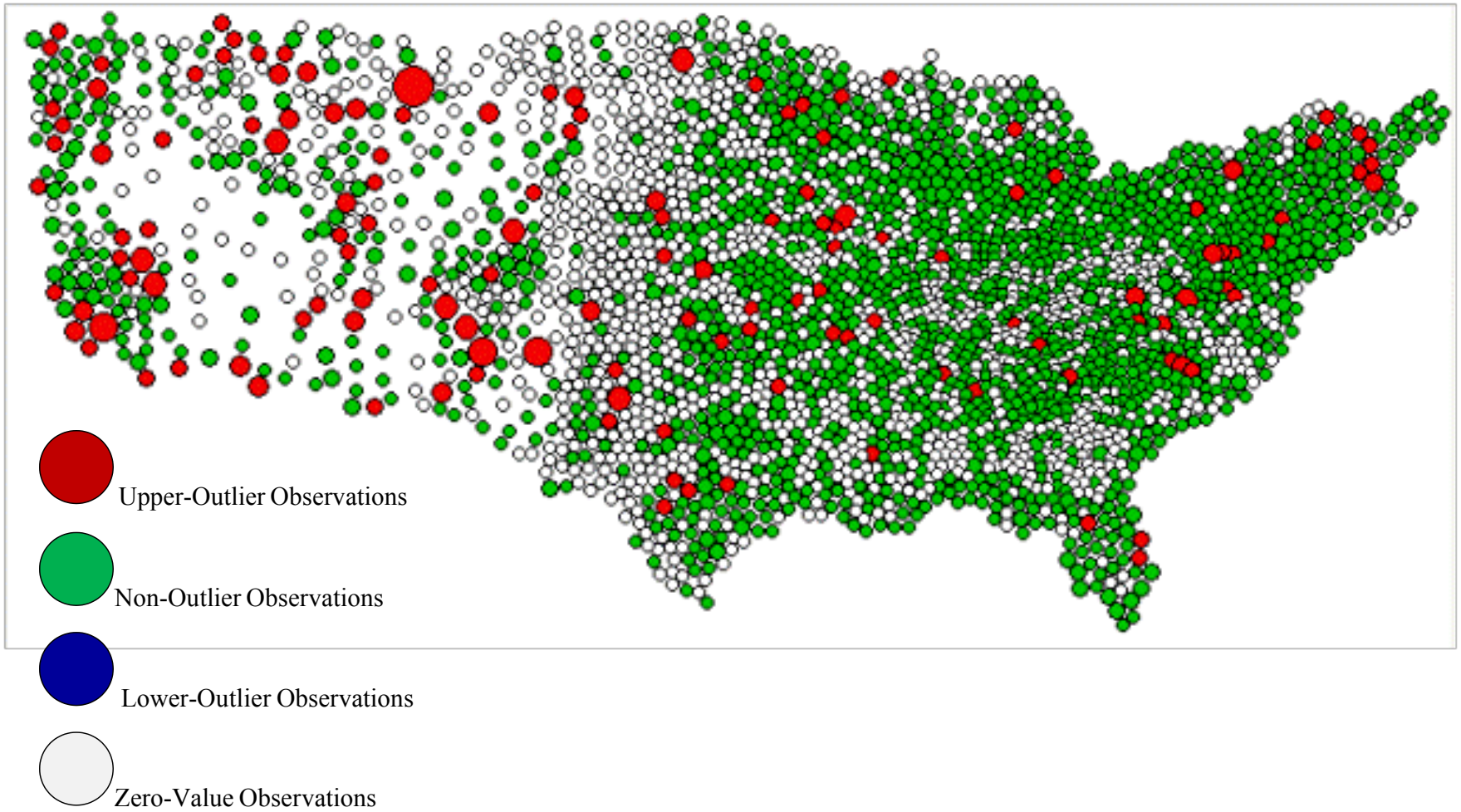
- Inability to push forward ground breaking discoveries, even from within the company, if they are not directly related to main business
- Christensen : The business options of successful companies are confined by their success
  - Big companies inevitably emphasize the needs of current customers and current product/service lines
  - Confirmed by R Henderson in 2006 study

Part 4: Let's revisit the "only in America" (or "only in Silicon Valley") argument

Rates of high technology company formation (# new firms formed annually / 1000 workers in each county) in US counties, shown as each county's percentile ranking among all US counties



U.S. counties sized by rates of high technology company formation (see previous slide)



Heavy concentration of Venture Capital investment in Silicon Valley

(source: Thomson Reuters Money Tree Report using data from Nat'l VC Association & PricewaterhouseCoopers)

vestments by Region / Q4 2011

Regions Defined	Total $ Invested	Average $ Per Deal	Deals
All	$6,565,830,700	$7,779,420	844

	Amount	% of Total	Deals
Silicon Valley	$3041M	46.32%	273
New England	$777M	11.84%	107
NY Metro	$545M	8.30%	82
LA/Orange County	$469M	7.15%	44
Texas	$306M	4.66%	31
San Diego	$269M	4.10%	23
Midwest	$201M	3.06%	48
DC/Metroplex	$179M	2.72%	45
Southeast	$177M	2.69%	40
Colorado	$166M	2.53%	27
Northwest	$137M	2.08%	34
Philadelphia Metro	$133M	2.02%	30
SouthWest	$63M	0.96%	19
North Central	$42M	0.64%	15
South Central	$38M	0.57%	22
Upstate NY	$23M	0.36%	4

Uniqueness of SV

NOT Creativity or entrepreneurship, instead:

- Large amounts of venture capital, often for later stage funding (growing a really bid company)
- Large numbers of mobile professionals

America – EU/Jpn differences less when comparing America outside of SV

Progress outside the USA

- Some impressive German and French biomedical startups
  - Including developing therapeutics (risky)
- Elana, Genmab and Aqtis from Utrecht University Department of Medicine
- Japan now in a second biotech IPO boom, also some very interesting companies

How do they do it?

- Variety of funding sources
  - Direct government funding and other support not particularly crucial.
- Often from a university laboratory
  - In Japan, a few examples of founders coming from a large company (Prism, Whill)
- Tapping into unmet demand
  - Unmet by large companies
- Less turnover among employees
  - Long term commitment, both ways
    - Example, Nintendo team that created SuperMario64

Part 5: Conclusions

New companies are important for innovation, but

- Viable variants exist to SV model
- Biggest difference between US and Europe/Jpn may be expectations regarding duration of employment
- For foreseeable future, Europe and Japan will depend relatively more on large companies for innovation

Countries should try to create an environment supportive of entrepreneurship without undermining established companies

- Capital markets
- Corporate governance
- Labor market reform
- University IP management policies to prevent companies from locking up IP
- Openness to foreign markets, investment and alliances
- However, governments' ability to target specific domestic industries for growth in technically advanced countries is doubtful
  - Innovation driven mainly by people responding to opportunities around them

Thank you for your attention and comments.

ご清聴ありがとうございました。コメントや感想を歓迎いたします。