

Box S4 | Special topic notes

Note 1: share of the pharmaceutical market. Various countries' shares of the 2005 world ethical pharmaceutical market compared with shares of discovery of all 252 drugs are provided in the table below:

Country/region	2005 pharmaceutical market (\$US billions)	% of 2005 world market	% share of discovery of all 252 drugs (Fig. 1)
US	250	44	47
Canada and Australia	24	4	3
Japan	60	11	9
UK	20	3.5	9
Germany	32	6	8
Switzerland	4.5	1	5
France	33	6	5
Other Europe	80	14	12
World total	570	100	100

Sources: For GDP, the World Bank. For pharmaceutical market: European, North American and world total sales are from www.imshealth.com. Japan, UK, German, and French sales are from the Japan Pharmaceutical Manufacturers Association, Data Book 2007, p. 54 (citing data from IMS World Review). The US:Canada sales breakdown is from Canadian Patented Medicines Prices Review Board, Annual Report 2005 at www.pmprb-cepmb.gc.ca (using IMS Health data). Swiss sales are from REF. 1.

Note 2: factors affecting pricing of new therapeutic biologics. Barriers to entry may be one reason for higher prices for new therapeutic biologics (NTBs) compared with small-molecule drugs. Among these barriers, higher company costs are associated not only with manufacturing but also (probably) development, and meeting regulatory approval standards. Discovery and development generally takes longer for NTBs than NMEs, and discovery and pre-clinical testing is probably more expensive on average for NTBs². Persons familiar with the biotech industry and the FDA approval processes maintain that NTBs often address more challenging diseases or more challenging therapeutic approaches than NMEs and also face a more complex approval process^{3,4}.

Note 3: orphan drug legislation in Japan and Europe. For orphan drugs in both Japan and the EU, the effective period of market exclusivity is ten years. This is based not on a prohibition against regulatory authorities approving the same drug to be marketed by a competitor for the same indication, but rather the inability of such a competitor to rely on the first applicant's data to assess safety and efficacy. Financial incentives vary between countries. For an English translation of the Japanese regulations, see Pharmaceutical Administration and Regulations in Japan at www.jpma.or.jp/english/parj/0607.html.

Note 4: approved orphan drugs in Europe and Japan. A list of orphan drugs that have received European marketing approval as of July 2008 is at http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_the_european_marketing_auth_Orphan_drugs.pdf. Although this list was not cross-checked against European approvals for non-orphan indications, it was cross-checked against FDA orphan and non-orphan approvals. One diagnostic agent, 5-aminolevulinic acid (for intra-operative photodynamic diagnosis of residual glioma) was excluded from analysis. It is unlikely that any of the European discovered orphan drugs discussed in this analysis has also been approved in Europe for non-orphan indications.

A complete list of the drugs accorded orphan status by the Japanese Ministry of Health, Labour and Welfare is at <http://www.nibio.go.jp/shinko/orphan/shitei.html>. There is no user-friendly public data base that shows approval dates for all indications (orphan as well as

non-orphan), so this information was obtained drug by drug to make sure the Japanese drugs classified as orphans in this analysis had not been approved in Japan for non-orphan indications..

Note 5: expenditure of selected countries on health-related R&D. The following table shows likely ranges of the percent of various countries' GDP accounted for by government funding of health-related R&D:

Country	Year	%GDP for that year, low estimate	%GDP for that year, mid-range estimate	%GDP for that year, high estimate
USA	2004	.231	.231	.231
Japan	2003	.023	.056	.090
Germany	2004	.026	.065	.104
UK	2002	.101	.127	.153
France	2003	.050	.087	.123
Canada	2002	.115	.152	.189

Sources: National Science Board for total government R&D and % to health and % to general university fund (GUF)⁵; World Bank for country and year-specific GDPs.

The reason for the range in estimates is that for all the listed countries (except the US where it is zero) a so-called general university fund (GUF) accounts for the largest percentage of government R&D expenditures. In Japan, GUF consists of block grants to universities to cover the salaries of permanent staff, infrastructure, etc., but not competitive or other project-specific research. In the case of Japan, a conservative estimate of the proportion of GUF devoted to health and other biomedical activities is one-third. Based on the author's knowledge of Japanese university budgets, a significant proportion of GUF does not support R&D. However, an explanatory note in REF. 5 indicates that most GUF listed in appendix table 4-47 does support R&D (implying that it is the R&D subset of total GUF). If this is the case, then the high estimate in the above table is the most accurate. The low estimate assumes that none of GUF supports R&D (highly unlikely, at least in the case of Japan). The middle estimate assumes that half of the GUF funding reported in REF. 5 supported R&D.

Note 6: career flexibility for biomedical researchers. In contrast to the United States, lifetime employment still prevails in most large Japanese and continental European manufacturing companies (especially among their R&D staff). This probably deprives biotechnology companies of the skilled R&D and management personnel they need to grow⁶⁻⁹.

Note 7: employee satisfaction. Surveys of employee job satisfaction have shown biotechnology companies generally scoring higher than established pharmaceutical companies^{10,11}. Another small survey of 26 entrants into Yale's molecular biophysics and biochemistry program in suggests that biomedical PhD graduates from such institutions might be more likely to be drawn to biotechnology companies rather than pharmaceutical companies¹². Of the 26 entrants in 1991 who earned Ph.D.s in 1997 or 1998, ten years later in 2008, more of them (10 in total) were working in biotechnology companies than any other type of organization. None was in a pharmaceutical company, although one worked in a pharmaceutical company for about two years before joining a biotechnology company¹².

Note 8: impact of the Bayh-Dole amendments in the United States. The 1980 Bayh-Dole amendments to US Patent Law (35 U.S.C. §§ 200-212) have been criticized for causing some US universities to place too much emphasis on obtaining license royalties¹³. Mowery and colleagues have also noted that university biomedical patent applications began to rise even before its enactment¹⁴. However, the formation of large numbers of biotechnology companies in the United States did not begin until after the Bayh-Dole amendments, suggesting that facilitating exclusive licenses of university discoveries to start-ups may be one of the primary benefits of this legislation^{6,15}.

Note 9: close relations between biotechs and universities, and the question of preferential access over pharmas. Shane, in reviewing licensing practices at MIT, concludes that large pharmaceutical companies often decline to license early-stage drug candidates or targets from universities, which end up licensing these to biotechnology companies as a last resort¹⁶. When the author worked in biomedical research and technology transfer in the US NIH from 1988 to 1997, licenses of candidate drugs and drug targets to established pharmaceutical companies were not uncommon. However, licensing officials at NIH reported in the period of this study that the majority licenses for NIH-discovered candidate drugs or drug targets were licensed to biotechnology companies owing to lack of interest from pharmaceutical companies in early-stage discoveries. One possible explanation is that it makes more sense for pharmaceutical companies to license from biotechnology companies than universities, because university discoveries are usually too early stage, whereas there is less uncertainty about university discoveries that have been developed by biotechnology companies and therefore they are more valuable for their company.

Another reason that pharmaceutical companies have given for preferring to develop in-house discovered drug candidates over those in-licensed from universities is that they retain greater control over the former. From the perspective of pharmaceutical companies, one of the most bothersome conditions in university licenses is the university's right to terminate an exclusive license if the pharmaceutical company is not developing a candidate drug and to re-license it to another company. However, universities also have a legitimate interest in preventing licensees that turn out not to be serious about inventing candidate drugs from using their license rights to prevent other companies from developing the drugs. Some pharmaceutical officials have noted that if the university license gives their company three years of exclusive control over the compound, this is sufficient, and beyond this time it would be reasonable for a university to request return of IP rights if the pharmaceutical licensee was not developing a drug candidate.

For an alternative perspective suggesting that US universities sometimes license biomedical discoveries to inventing professors' start-ups without carefully considering whether existing companies might be more willing and capable to develop the discoveries, see REF. 15. In any case, close relationships with universities have been essential to the growth of many biotechnology companies¹⁶⁻²².

Also, at least in Canada, an additional factor may be explicit policies by both national and provincial governments to foster the growth of innovative new companies so as to keep as much of the value added development of Canadian university discoveries in Canada. Even in US universities, regional development objectives sometimes favour licensing to local start-ups. Also the Bayh-Dole regulations (37 C.F.R. § 401.14(k)(4)) call for licensing of US government-funded university inventions preferentially to small businesses.

Nevertheless, based on the evidence overall, these preferences probably do not result in many university pharmaceutical discoveries being licensed to biotechnology companies when pharmaceutical companies were also competing for the license. Further evidence to clarify this issue would be welcome.

Note 10: biotechnology companies in Japan. The data presented are based primarily on the author's analysis of the pipelines of each of the 160 companies that listed a therapeutic field as their primary or secondary business focus in the latest (2008) survey of Japanese biotechnology companies by the Japan BioIndustry Association²³. The company totals include five companies whose lead compound is a cancer vaccine or another immunostimulatory therapy for cancer and one whose lead compound relates to gene therapy for peripheral artery disease. If regenerative medicine therapies are included in the analysis, there were 24 Japanese biotechnology companies with 38 drugs or pharmaceutical therapies on the market (4) or in clinical trials. If drug delivery systems/technologies (DDS) are also included, there were 27 Japanese biotechnology companies with 46 therapies on the market (6) or in clinical trials.

Note 11: efficiency of a system of biotechnology companies. It has been suggested that a large number of independent biotechnology companies developing drugs is an inefficient system, and that this system discovers a large number of innovative drugs because a large number of companies are able to pursue many more leads than established pharmaceutical companies.

While not disputing this assertion, with respect to numbers of companies the number of biotechnology companies worldwide is probably close to 5,000, but the total number in the US (the locus of most biotechnology company drug discovery) is only about 1,500 (<http://bio.org/ata glance/>), not all of whom are focused on pharmaceutical R&D.

With respect to efficiency, DiMasi's 2007 study² suggests slightly higher costs associated with development of biotech drugs, while also indicating that it takes longer to develop biotech drugs. Pisano presents data indicating that total R&D costs per new drug are approximately equal between biotechnology companies and pharmaceutical companies, whether analyzed on an industry wide or individual firm basis¹⁵. Neither of these studies distinguished between innovative and non-innovative drugs.

As for the likelihood of inefficiencies associated with biotechnology companies operating independently, Saxenian^{24,25}, Hyde⁸ and REFS 16-22 suggest a high degree of communication among biotechnology companies, between biotechnology companies and universities, and (at least in successful drug development efforts) between biotechnology companies and pharmaceutical companies. Frequent job transfers among biotechnology companies, close ties with universities, and sharing common academic and industry advisors, contribute to the communication network. So, the concern that the independence of biotechnology companies, in and of itself, increases inefficiency due to lack of coordination or information exchange is questionable. Moreover, a recent analysis by Munos²⁶ indicates that new drug approvals increase greater than linearly (probably exponentially) with the number of companies engaged in drug discovery.

In light of the probable rough equivalency in overall efficiency between pharmaceutical companies and biotechnology companies, this study suggests not simply that more companies are likely to pursue more leads. It also suggests that it often makes a difference whether bright scientists must spend their time in large organizations or whether they have the resources to work relatively independently.

Note 12: examples from Japan of the potential significance of drugs discovered, at least in part, by university researchers but not approved in the United States. Among the Japan discovered orphan drugs approved for sale in Japan, non-recombinant human activated protein C was discovered by the university-affiliated and not-for-profit Chemo-Sero-Therapeutic Research Institute in Kumamoto. However, as discussed in Supplementary Information S3 (box), note 13, it is unlikely that it will be marketed in the United States. Among the six Japanese biotech drug delivery, regenerative medicine and pharmaceutical therapies marketed in Japan (see Supplementary Information S4 (box), note 10), two are LTT Bio-Pharma's lipid microsphere formulations of prostaglandin E1 and dexamethasone. These formulations were developed with assistance from scientists in St. Marianna Medical University in Tokyo. However, neither LTT Bio-Pharma, nor Taisho or Mitsubishi-Tanabe Pharma which hold Japan marketing rights, probably have plans to apply for approval in the United States.

However, some drugs that may not seem likely candidates for FDA approval are eventually approved. One example may be pitivastatin, which was originally discovered by Nissen Chemical's pharmaceutical division with help from University of Tokyo researchers. It was approved in Japan in 2003. Novartis, (which had rights from Kowa Pharmaceuticals which had acquired rights from Nissen) dropped development and returned rights to Kowa, which pursued development. The FDA approved the NDA in August 2009 under *standard* review, and pitivastatin (brand name Livalo) joined at least six other statins approved in United States. It may have a relatively good drug interaction profile

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