The importance of new companies for drug discovery: origins of a decade of new drugs

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Abstract | Understanding the factors that promote drug innovation is important both for improvements in health care and for the future of organizations engaged in drug discovery research and development. By identifying the inventors of 252 new drugs approved by the US Food and Drug Administration from 1998 to 2007 and their places of work, and also classifying these drugs according to innovativeness, this study investigates the contribution of different types of organizations and regions to drug innovation during this period. The data indicate that drugs initially discovered in biotechnology companies or universities accounted for approximately half of the scientifically innovative drugs approved, as well as half of those that responded to unmet medical needs, although their contribution to the total number of new drugs was proportionately lower. The biotechnology companies were located mainly in the United States. This article presents a comprehensive analysis of these data and discusses potential contributing factors to the trends observed, with the aim of aiding efforts to promote drug innovation.

The current environment for drug research and development (R&D) is characterized by major challenges, including pharmaceutical industry pipelines that are insufficient to replace revenues from drugs that are becoming generic, diminishing venture capital funding for early-stage companies and mounting criticism of university technology licensing practices. Understanding the factors that promote the discovery and development of new drugs — particularly truly innovative drugs that respond to unmet medical needs — could have an important role in developing strategies to address these challenges.

One such factor is the types of environment, both organizational and regional, that are most conducive to innovative drug R&D. With this in mind, this article presents an analysis of the origins of 252 new drugs that were approved by the US Food and Drug Administration (FDA) from 1998 to 2007, which represent almost all the new drugs approved during this period that are regulated by the FDA's Center for Drug Evaluation and Research (CDER). The drugs are classified according to whether they are scientifically innovative and whether they respond to unmet medical needs. The relative contributions of pharmaceutical companies, biotechnology companies and universities to the discovery of each drug are quantified, thereby illustrating their relative contributions to new drug approvals overall during this period. In addition, the countries where the discoveries occurred are identified, which could help to clarify the institutional and policy environments that favour innovative drug discovery.

Previous analyses (for example, REFS 1–4) have noted the importance of new companies for drug discovery, but have not based their analysis on the place of invention and/or have not tried to assess medical or scientific innovativeness. Ultimately, this study rests upon the validity of its methodology (BOX 1; see Supplementary information S1 (box), notes 1-8), in particular the accuracy of the attributions and the innovativeness classifications. These are summarized in TABLE 1 and detailed in Supplementary information S2 (table) for each of the 252 drugs. Ensuring the validity of these classifications has been a primary goal of this research (some initial findings of which, discussing FDA approvals between 1998 and 2003, have been previously published[5,6]). However, there are inherent limitations in the understanding of the histories of these drugs and also in the methodology (BOX 2). In particular, by focusing on the discovery of the active compounds, the analysis inevitably overlooks important preceding research as well

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as subsequent translational and development research. Moreover, the analysis covers a relatively short period, and system-wide changes in recent years — such as a prolonged decline in early-stage venture capital funding and closer collaboration between pharmaceutical companies and universities — may mean that the phenomena described are transitory. Nevertheless, it is hoped that this analysis will assist all stakeholders in drug discovery and development in identifying and supporting the environments and organizations that promote early-stage pharmaceutical innovation in the next decade.

Box 1 | **Data sources and analysis**

Drugs analysed

The initial list of new drugs analysed in this study were obtained from the US Food and Drug Administration (FDA) website (see Supplementary information S1 (box), note 1). The basic sample consists of 252 new drugs approved by the FDA between 1998 and 2007, 215 of which were approved under New Drug Applications (NDAs) as new molecular entities (NMEs) and 37 of which were approved under Biologics Licence Applications (BLAs) (see Supplementary information S1 (box), notes 1 and 2). In order to analyse only new therapeutics that represent biochemical inventiveness over previously known compounds, a further 22 compounds approved by the Center for Drug Evaluation and Research (CDER) in this time — such as diagnostic imaging agents — were excluded from the analysis (see Supplementary information S1 (box), note 3).

Classification of drugs

Between 1998 and 2007, the CDER classified NMEs according to whether they were anticipated to offer substantial therapeutic benefits over currently marketed drugs. The FDA granted such NMEs a priority review and others a standard review, and this study designates these drugs as pNMEs and sNMEs, respectively. Of the 215 NMEs analysed, 117 are sNMEs and 98 are pNMEs. Drugs submitted under BLAs, at least after 2003, were also granted priority or standard reviews: of the 37 new therapeutic biologics (NTBs), 24 were probably granted a priority review. The type of review for two others is uncertain, although it was probably a standard review (see Supplementary information S2 (table)). This distinction for the NTBs is not generally applied in this study (see Supplementary information S1 (box), note 4).

In addition, all drugs were classified according to whether they were scientifically novel — that is, whether their mechanisms of action were novel and/or whether they were the first in a distinct class of compounds at the time of approval. Either criterion was satisfied if the drug was approved within 3 years of the approval of the first drug with the same mechanism of action in the same chemical family (see Supplementary information S1 (box), note 4). According to this test, 118 drugs were classified as novel and the remaining 134 drugs were classified as follow-ons.

Drug origins and attributions

The origins of the drugs analysed were determined by identifying the inventors and their places of employment. This enabled the attribution of discovery according to country and type of organization (see Supplementary information S1 (box), note 5, for further details on the definition of organization types), namely:

- Large established companies, described as pharmaceutical companies in the main text. These are usually pharmaceutical companies, but in some cases are pharmaceutical divisions of an established company whose main line of business is in another industry;
- Small established pharmaceutical companies, with <1,000 employees at time of drug discovery;
- New companies (formed after 1975) focused on drug discovery, described as biotechnology companies in the main text, some of which are primarily engaged in small-molecule drug discovery, rather than protein therapeutics harnessing recombinant DNA technology;
- Academic or other not-for-profit research organizations whose initial development partner was a pharmaceutical company (denoted U→P in the main text) or whose initial development partner was a biotechnology company (denoted U→B in the main text).

Various sources — principally patents, scientific articles, business articles and US Securities and Exchange Commission reports — helped determine which companies first began to develop university-discovered drugs (see Supplementary information S1, note 6).

The first step in identifying inventors was to find the key patents covering each drug. For each of the 215 NMEs, the patents covering the chemical structure of the final compound, the compounds directly preceding discovery of the final compound and the discoveries that demonstrated therapeutic proof-of-concept for a disease that is a principal target of the final drug (preferably *in vivo*) were investigated, using sources including the FDA Orange Book, the FDA Administrative Correspondence associated with drug approval, and the Merck Index (see Supplementary information S1 (box), note 7). These constituted the key patents for each NME. The preferred sources to determine employment of the inventors at the time of discovery were scientific articles co-authored by the inventors on topics related to the drug and submitted for publication within a few years of the patent application date.

After determining the place where each inventor worked at the time of discovery, each family of key patents was apportioned according to the type of inventing institution and country of invention. In this process, multiple inventors on a single patent were each weighted equally. Then, using the weights described in Supplementary information S1 (box), note 7, for each family of key patents, each drug was accorded the value '1', which was apportioned twice: once according to type of inventing institution and once according to national origin. In the case of drugs without key patents, the same process was applied to the families of key scientific articles and their authors. These allocations are shown in the first two tables in Supplementary information S2 (table). Unless otherwise indicated, numbers in this study refer to whole drug equivalents (WDEs).

The FDA does not require applicants who are seeking approval of NTBs to disclose the covering patents. However, REF. 23 describes the early development history of most of the NTBs and usually indicates the key patents and key transfers of technology underlying each NTB. This was used as a starting point for identifying and weighting the key patents. Because many of the NTBs combine distinct technologies, attributing the discovery of NTBs sometimes required an understanding of the histories of several core technologies and the weighting of several families of relevant patents (see Supplementary information S1 (box), note 7).

TABLE 1 presents a summary of the data. A complete description is provided in Supplementary information S2 (table), in which the discovery of each of the 252 drugs is attributed proportionally according to both country and type of discovering organizations. The tables list all 252 drugs by their trade and generic names, year of FDA approval, classification as NME or NTB, review priority status, whether they are scientifically novel, whether they are approved only for orphan indications, the main inventing organizations and their type, the year of peak sales, the sales during peak year (see FIGS 4–6 and Supplementary information S1 (box), note 8), and main therapeutic indication, including a brief summary of the mechanism of action. Additional explanations for particular drugs or groups of drugs are provided in Supplementary information S3 (box).

Table 1 | **New drugs approved by the FDA CDER from 1998 to 2007 by type and discovering organization***

Drug classification	Pharmaceutical company‡	Biotechnology company	University; first transfer to a pharmaceutical company§	University; first transfer to a biotechnology company‖	Total
Original CDER classification					
sNMEs	87.7 (75%, 60%)	8.8 (7%, 20%)	9.2 (8%, 43%)	11.4 (10%, 29%)	117 (46%)
pNMEs¶	55.4 (57%, 38%)	15.4 (16%, 35%)	9.1 (9%, 43%)	18.0 (18%, 46%)	98 (39%)
NTBs	4.0 (11%, 3%)	19.9 (54%, 45%)	3.1 (8%, 14%)	10.0 (27%, 25%)	37 (15%)
After reclassifying 21 polypeptide and two polynucleotide NMEs as NTBs					
sNMEs	83.7 (79%, 57%)	6.4 (6%, 14%)	7.2 (7%, 34%)	8.7 (8%, 22%)	106 (42%)
pNMEs¶	52.2 (61%, 35%)	9.3 (11%, 21%)	8.6 (10%, 40%)	15.9 (18%, 40%)	86 (34%)
NTBs (expanded)	11.2 (19%, 8%)	28.4 (47%, 64%)	5.6 (9%, 26%)	14.7(25%, 37%)	60 (24%)
All drugs (including NTBs) classified according to review priority‖					
Standard	90.5 (70%, 62%)	15.2 (12%, 35%)	10.2 (8%, 48%)	13.0 (10%, 33%)	129 (51%)
Priority¶	56.6 (46%, 38%)	29.0 (23%, 65%)	11.2 (9%, 52%)	26.3 (21%, 67%)	123 (49%)
All drugs classified according to scientific novelty					
Follow-ons	95.6 (71%, 65%)	14.2 (11%, 32%)	12.0 (9%, 56%)	12.2 (9%, 31%)	134 (53%)
Scientifically novel	51.5 (44%, 35%)	29.9 (25%, 68%)	9.4 (8%, 44%)	27.2 (23%, 69%)	118 (47%)
Overall					
Orphan drugs	15.6 (29%, 11%)	12.0 (22%, 27%)	6.7 (12%, 33%)	19.6 (36%, 49%)	54 (21%)
Total	147.2 (58%)	44.1 (18%)	20.4 (8%)	40.3 (16%)	252

CDER, Center for Drug Evaluation and Research; FDA, Food and Drug Administration; NME, new molecular entity; NTB, new therapeutic biologic; p, priority review; s, standard review. See BOX 1 for an explanation of the definitions. *Numbers represent whole drug equivalents (WDEs). Percentages in brackets indicate, first, the proportion of the type of drug indicated by the row label that are discovered by the type of discovering organization indicated by the column heading and, second, the proportion of the drugs discovered by the type of organization indicated by the column heading that are the type of drug indicated by the row label. ‡Includes 6.4 WDEs discovered by small pharmaceutical companies. §Includes 1.5 WDEs discovered by universities and transferred to small pharmaceutical companies. ‖Rasburicase (Elitek) and omalizumab (Xolair) are assumed to have received standard review. ¶Priority review by the FDA implies substantial benefit over currently marketed drugs.

Origins of new drugs

Number and key characteristics of new drugs. A summary of the characteristics of the new drugs approved in the period studied is presented in TABLE 1. Each type of organization was attributed a proportion of the discovery of each new drug based on the extent of its contribution (see Supplementary information S2 (table)), which was determined through investigation of the associated patents and research (BOX 1; see Supplementary information S1 (box), note 7). The values in the tables therefore represent whole drug equivalents (WDEs), and so are not necessarily integers.

Overall, of the 252 drugs studied, pharmaceutical companies were attributed 147.2 WDEs (58%), biotechnology companies were attributed 44.1 WDEs (18%), universities that transferred their discoveries to biotechnology companies (U→B) were attributed 40.3 WDEs (16%), and universities that transferred their discoveries to pharmaceutical companies (U→P) were attributed 20.4 WDEs (8%).

Two key characteristics of the 252 drugs were also analysed: the extent to which they addressed unmet medical needs and their scientific innovativeness. The assignment of priority review status by the FDA, which is granted to drugs that are anticipated to provide substantial benefit over currently marketed drugs, was used as an indicator for the first characteristic. Considerations related to the novelty of the mechanism of action and/or the chemical structure of the drug were used for the second characteristic (BOX 1; see Supplementary information S1 (box), note 4).

With regard to addressing unmet medical needs, of the 123 drugs in the priority review category, 56.6 WDEs (46%) were attributed to pharmaceutical companies, and 66.4 WDEs (54%) were attributed either to biotechnology companies (29.0 WDEs; 23%) or universities (37.5 WDEs; 30%) (TABLE 1). In addition to the important finding that biotechnology companies or universities provided more than half of the overall discovery contribution for drugs in this category, it is also noteworthy that a substantially greater proportion of the total number of WDEs attributed to biotechnology companies and universities are in this category, rather than the standard review category. For example, 65% of the WDEs attributed to biotechnology companies are for the 123 drugs in the priority review category, with 35% in the standard review category, whereas the corresponding figures for pharmaceutical companies are 38% in the priority review category and 62% in the standard review category.

In the assessment of scientific innovativeness, of the 118 drugs considered to be scientifically novel, 51.5 WDEs (44%) were attributed to pharmaceutical companies, and 66.5 WDEs (56%) were attributed either to biotechnology companies (29.9 WDEs; 25%) or universities

Box 2 | **Limitations of this analysis**

Because this analysis focuses on drugs approved by the US Food and Drug Administration (FDA) for the US market, it inevitably misses drugs originating in Europe, Japan and elsewhere for which FDA approval has not been sought. With regard to the validity of this study's conclusions, the crucial issue is the proportion of these missed drugs that would be classified as scientifically novel or as priority-approved new molecular entities (pNMEs) or new therapeutic biologics. In this respect, although it is possible to identify several Japanese drugs for which overseas marketing approval has not been sought, including a few whose discovery involved university researchers (see Supplementary information S4 (box), note 12), it seems unlikely that any would be considered scientifically novel or be granted priority review by the FDA. In addition, the lists of orphan drug approvals for both Japan and Europe provide comprehensive lists of recently approved drugs for niche indications. The fact that all the European orphan drugs have either been approved by the FDA or (with one possible exception) are advanced in the FDA application process suggests that, even in the case of drugs with limited markets, European drugs that are scientifically novel or offer new health benefits are likely to also be approved in the United States. The same probably applies to orphan drugs from Japan.

Another limitation is that some significant contributions by university researchers may have been overlooked, particularly in the case of drugs attributed to European pharmaceutical companies. The various steps described in the methods (BOX 1 and Supplementary information S1 (box)), are intended to limit this possibility. However, because limited use was made of sources in languages other than English or Japanese, references to continental European academics contributing to the discovery of some drugs may have been missed.

There were several challenging decisions regarding classification of particular drugs as scientifically novel or follow-ons. Readers with questions about the criteria and any particular classifications are directed to Supplementary information S1 (box), note 11. Estimating the sales of some drugs was also challenging (see Supplementary information S1 (box), note 8), and, in general, peak annual sales are not a perfect metric to assess overall market value.

There are conceptual and philosophical issues related to defining and assessing discovery. A preliminary analysis[5,6] focused only on patents. However, a more comprehensive approach is to integrate information on the patent inventors with scientific articles, often written by the same inventors. It was reassuring that, in many cases, both the articles and patents indicated the same researchers and organizations were responsible for the discovery of the core active compounds and proof-of–concept studies. Nevertheless, judgment calls were necessary when researchers in more than one organization contributed significantly to discovery, and also when a core compound had been known and the key step in discovery was the recognition that the compound had a new therapeutic use.

Finally, discovery of the core compounds, or of new therapeutic uses for old compounds, is only one aspect of drug discovery and development — perhaps not even the most important or difficult part. This analysis inevitably ignores many insightful discoveries that lead to the discovery of the final compounds. It overlooks the challenges in altering initial candidate compounds to make them more effective, safe and easy to manufacture and use, as well as the challenges in conducting clinical trials. It only tangentially addresses the importance and complexity of companies' decisions to go forward with development once lead compounds are discovered.

An account[24] of the years of fundamental and clinical research that contributed to the discovery and development of HIV integrase inhibitors (of which raltegravir (Isentress, a pNME approved in 2007) is the first approved) is just one of many articles showing the important nuances that this analysis could not adequately accommodate. A complementary analysis might apply bibliographic and social networking tools to link the key patents and articles for each drug with the articles and patents that reference them and that they cite[25]. This would provide a picture of the interconnections between the discoveries of some of these drugs and further insights into the key organizations that contribute to discovery.

(36.6 WDEs; 31%) (TABLE 1). Thus, biotechnology companies and universities provided more than half of the discovery contribution to scientifically innovative drugs. Similarly, a substantially greater proportion of the WDEs attributed to biotechnology companies and universities transferring to biotechnology companies are scientifically novel (68% and 69%, respectively) rather than follow-on products. The opposite is true for the WDEs attributed to pharmaceutical companies, with 65% of these WDEs corresponding to follow-on products (TABLE 1).

The data also show that biotechnology companies rather than pharmaceutical companies tended to undertake early development of innovative university drugs. A comparison of the entries in TABLE 1 for U→B drugs with those for U→P drugs shows that biotechnology companies undertook the initial development of the majority of university-discovered drugs that were scientifically novel (74%) or offered substantial benefit over existing drugs (70%). By contrast, pharmaceutical companies and biotechnology companies shared approximately equally in the initial development of university-discovered drugs that were not priority reviewed, and scientific follow-ons.

Small, established pharmaceutical companies contributed to the discovery of seven of the 252 drugs (five of which are for neurology indications). Of these seven, the majority are follow-ons and only one was granted priority review. This suggests that small, established pharmaceutical companies are no more likely than pharmaceutical companies as a whole to discover innovative drugs. The same applies to drug discovery by companies whose main area of business is not pharmaceuticals, nine of whose drugs are included in this analysis (see Supplementary information S3 (box), note 3).

Regional trends. The cross-tabulations in Supplementary information S2 (table) summarize the WDE attributions by type of drug, inventing organization and country of origin. Key findings are highlighted in FIGS 1–3. Interestingly, the overall discovery shares are close to

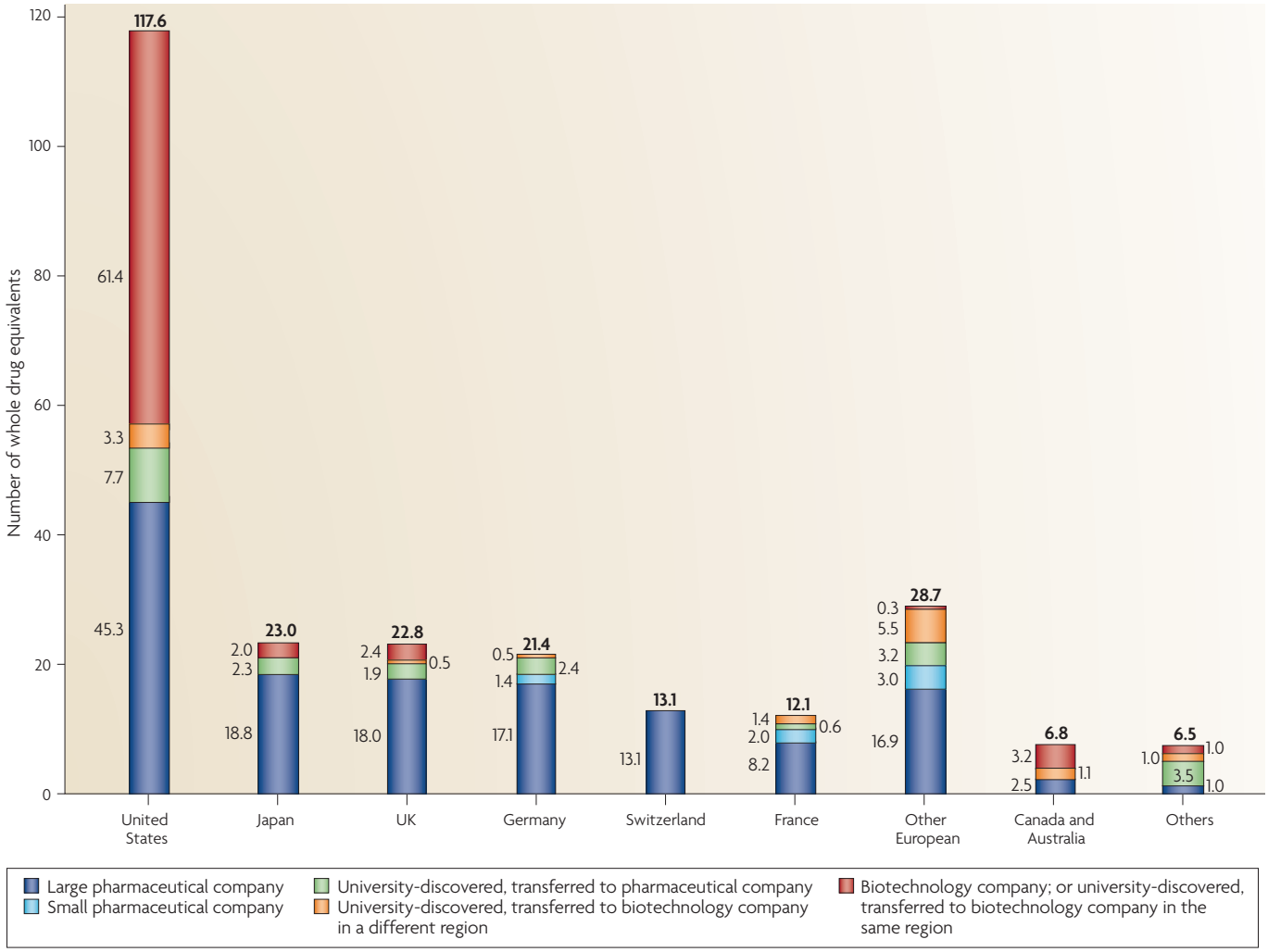

Figure 1 | **Allocation of the 252 new drugs approved by the US Food and Drug Administration between 1998 and 2007.** The distribution of the discovery of all 252 drugs according to the type of the discovering organization (see key) among the six leading drug-discovering countries (United States, Japan, UK, Germany, Switzerland and France), other countries in continental Europe (principally Italy, Denmark, Belgium, Sweden, the Czech Republic and Spain), Canada and Australia combined and other countries (principally Israel). The numbers represent whole drug equivalents; for details, see BOX 1 and Supplementary information S1 (box).

each country's share of the 2005 world pharmaceutical market, except for the UK and Switzerland, which substantially exceed their market shares (see Supplementary information S4 (box), note 1). In all but a few countries, pharmaceutical companies discovered the overwhelming majority of drugs (FIG. 1). The most notable exception is the United States, which accounted for the discovery of nearly half (117.6 WDEs) of the 252 drugs studied. Here, over 60% of the attributed WDEs were for drugs discovered in universities or biotechnology companies.

In most other countries, the majority of drug discovery occurred in the in-house laboratories of large pharmaceutical companies (FIG. 1). When considering the number of WDEs discovered outside pharmaceutical companies, the only countries in which biotechnology companies and/or universities made a notable contribution (>1 WDE) are the UK (4.8 WDEs; 1.6 from biotechnology companies), Japan (4.3 WDEs; 2 from biotechnology companies), Israel (3.7 WDEs; 3.2 from universities), the Czech Republic (3.1 WDEs from universities), Germany (2.9 WDEs from universities), Canada (2 WDEs from universities), Australia (2.3 WDEs; 2.1 from universities), France (1.9 WDEs from universities) and Sweden (1.75 WDEs from universities). It is also notable that only in Australia, Canada and Israel did the contribution from universities and biotechnology companies outweigh or approach that of pharmaceutical companies (see Supplementary information S3 (box), note 4). It is probably not a coincidence that in these three countries, and of course also the United States, the proportion of drugs discovered in universities is higher than in other countries.

Nearly 80% of drugs discovered in US, Australian and Canadian universities were transferred to biotechnology companies. Biotechnology companies (mainly in the United States) developed about half of the university drugs from outside these three countries, but they

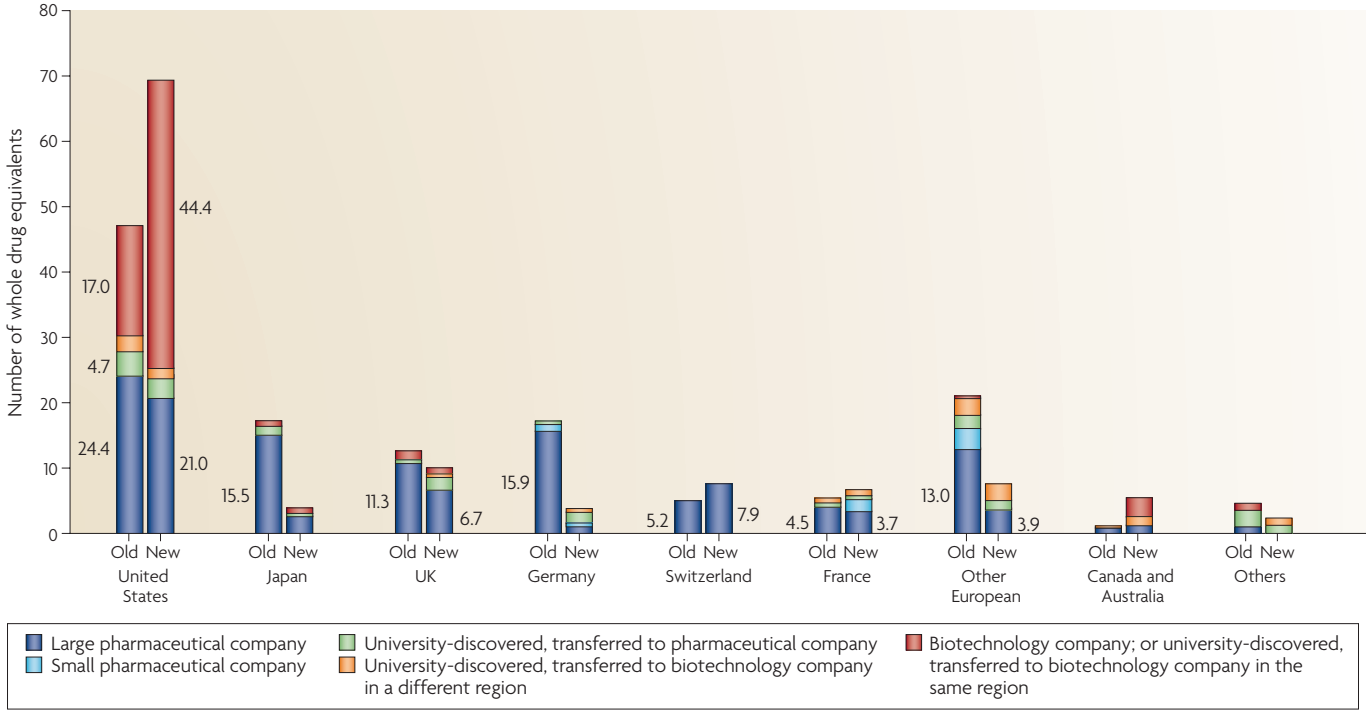

Figure 2 | **Distribution of the 252 new drugs approved by the US Food and Drug Administration between 1998 and 2007 according to scientific novelty.** For each discovering country or region, the figure shows the distribution of the discovery of the overall set of drugs according to the type of discovering organization (see key), as in FIG. 1, with an additional classification based on whether the drugs are scientifically novel (new) — for example, those with a new mechanism of action — or follow-on products (old). The numbers represent whole drug equivalents; for details, see BOX 1 and Supplementary information S1 (box).

tended to develop the more innovative of these products (see Supplementary information S3 (box), note 5).

The regional analysis suggests that countries where biotechnology companies and universities transferring to biotechnology companies are active in drug discovery are also countries with high proportions of scientifically or medically innovative drugs. FIGURE 2 shows that, in the United States, most of the scientifically innovative drugs (BOX 1) were discovered in biotechnology companies or in universities transferring to biotechnology companies. The same trend was seen, although on a much smaller overall scale, in Australia and Canada. Elsewhere, only in Switzerland and France did the number of scientifically innovative drugs exceed the number of follow-ons. In every major pharmaceutical country, most follow-on drugs were discovered in pharmaceutical company laboratories.

A similar pattern emerges when comparing standard new molecular entities (sNMEs), priority-reviewed new molecular entities (pNMEs) and new therapeutic biologics (NTBs) (FIG. 3). Most drugs attributed to the United States are pNMEs (55.2 WDEs) or NTBs (30.3 WDEs), representing 73% of the total. pNMEs and NTBs also account for 70% of Australia and Canada's total. By contrast, sNMEs constitute a clear majority in other regions except in Switzerland and France, where they account for about half of all drugs. However, even in the United States, most sNMEs were discovered in major pharmaceutical companies.

The discovery of NTBs was dominated by US biotechnology companies and US universities that partnered with biotechnology companies (see Supplementary information S3 (box), note 6). Cambridge Antibody Technology was the only non-US biotechnology company that contributed substantially to the discovery of an NTB — adalimumab (Humira) — which was approved in 2002.

Sales of new drugs

So far, this analysis has dealt only with the numbers of drugs discovered in the period of study, and not their commercial value. In this respect, one question is whether the trends observed with regard to the discovering organization (TABLE 1) reflected a tendency for pharmaceutical companies to focus discovery resources on drugs that are likely to provide large revenues, and whether many of the large-revenue drugs were not scientifically innovative or, more counter-intuitively, did not respond to unmet medical needs. In this scenario, a related question is whether the drugs discovered at biotechnology companies and universities, although more likely to be novel and/or respond to unmet needs (TABLE 1), are also more likely to have lower sales than drugs discovered in pharmaceutical companies.

To investigate these questions, sequential data on annual worldwide sales were obtained, and peak year sales within the 1999–2008 period were used as an indicator of market value for each of the subset of 214 drugs

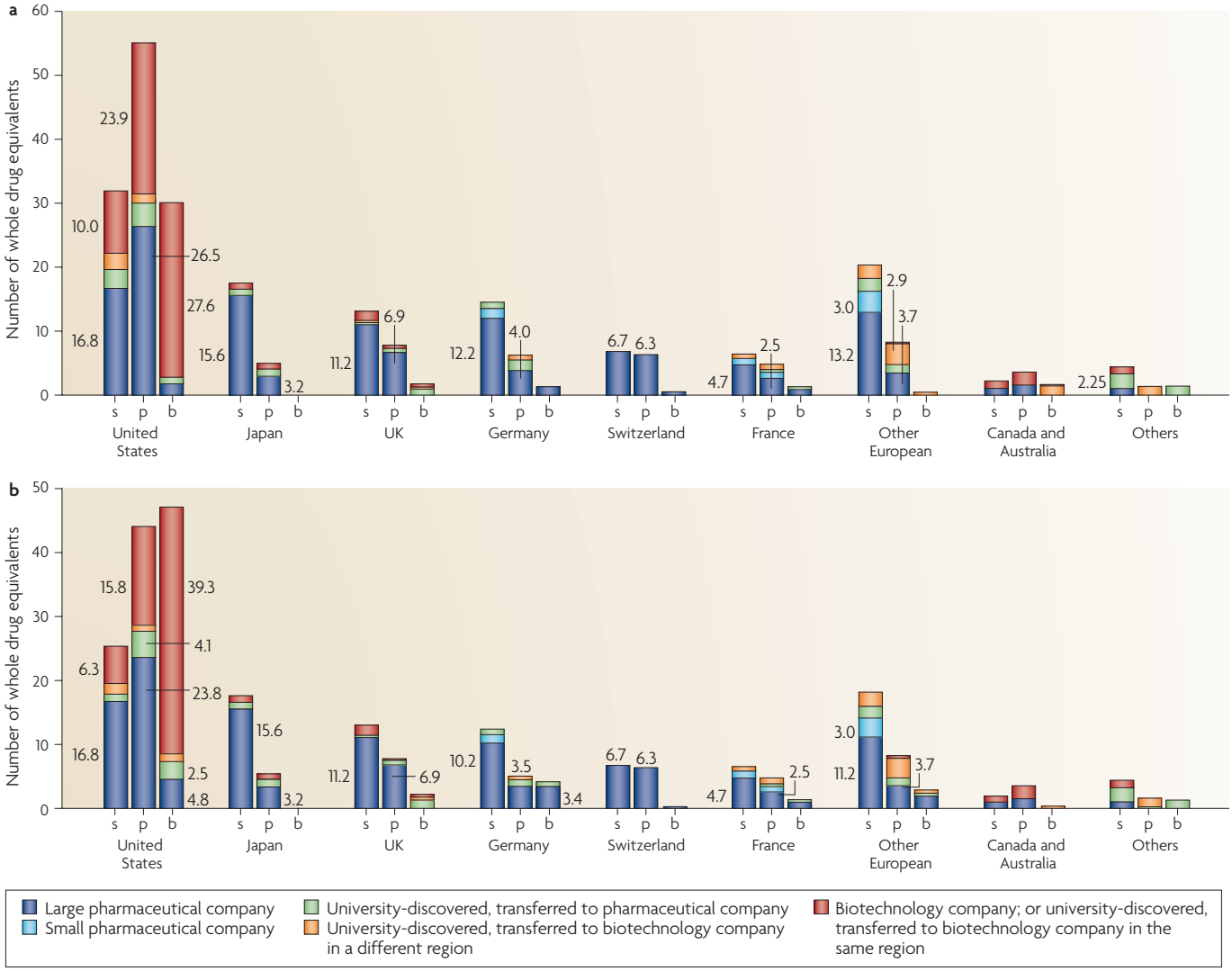

Figure 3 | **Distribution of the 252 new drugs approved by the US Food and Drug Administration between 1998 and 2007 according to regulatory review priority.** For each discovering country or region, the figure shows the distribution of the discovery of the overall set of drugs according to the type of discovering organization (see key), as in FIG. 1, with an additional classification based on whether the new molecular entities (NMEs) were granted a standard (s) review or a priority (p) review by the FDA. New therapeutic biologics (b) are considered separately; in part **a**, the data for the 37 new therapeutic biologics approved under Biologics Licence Applications are shown, whereas part **b** shows data for an expanded set of 60 new therapeutic biologics that also includes 23 polypeptide-based or polynucleotide-based NMEs. The numbers represent whole drug equivalents; for details, see BOX 1 and Supplementary information S1 (box), note 2.

now regulated by CDER that were approved between 1998–2005 (this shorter time frame allowing at least 3 years for sales to gain momentum (BOX 1; see Supplementary information S1 (box), note 8)). These sales were then allocated by region and type of discovering organization in the same manner that discovery was attributed for the individual drugs.

Sales trends for discovering organizations. The mean peak year (MPY) sales of the 214 drugs are presented in TABLE 2. The highest MPY sales are for drugs discovered by biotechnology companies (US$1.22 billion), which are considerably higher than those discovered by pharmaceutical companies ($0.85 billion). MPY sales for U→P drugs are slightly lower ($0.75 billon), whereas those for U→B drugs are substantially lower ($0.32 billion). Follow-on drugs have slightly higher MPY sales than scientifically novel drugs ($0.85 billion compared with $0.79 billion), and similarly MPY sales are only modestly higher for sNMEs than pNMEs. So, at first glance, there seems to be little evidence for the hypothesis that pharmaceutical companies primarily discover drugs that have high MPY sales whereas other organizations discover drugs with lower MPY sales, or that there is a substantial difference in the MPY sales of scientifically innovative and follow-on drugs that might help explain the trends shown in TABLE 1.

However, NTBs have considerably higher MPY sales than any other category of drugs (nearly 40% are blockbusters, although about one-third have peak annual sales

Table 2 | **Mean peak year sales (US$ millions) of 214 drugs approved from 1998 to 2005**

Type of drug (number of drugs)	Mean values by discovering organization				Total mean values	Value < $100 million/ value > $1,000 million (%)
	P+P_S (125.4)*	B (36.94)*	U→(P+P_S) (18.75)*	U→B (32.91)*		
Original CDER classification by pNME, sNME or NTB						
sNME (98)	915	263	325	220	772	27/24
pNME (85)	737	438	958	211	605	36/22
NTB (31)	949	2,228	1,218‡	644	1,587	26/39
As above, with NTBs expanded to include all polypeptide and polynucleotide drugs						
sNME (88)	881	246	371	153	772	26/25
pNME (73)	780	693	1,020	215	682	33/26
NTB expanded (53)	927	1,530	828	509	1,105	34/26
Classification by scientific novelty						
Follow-on (116)	865	1,208	859	319	852	26/29
Novel (98)	821	1,226	589	320	790	36/21
*Classification by scientific novelty, NMEs only**						
Follow-on NME (108)	843	398	788	230	764	27/27
Novel NME (75)	858	380	486	206	598	37/19
Overall						
Orphan drugs (44)	561	876	412	132	470	52/17
Total (214)*	850	1,220	746	319	823	30/26

B, biotechnology company; CDER, Center for Drug Evaluation and Research; FDA, Food and Drug Administration; NME, new molecular entity; NTB, new therapeutic biologic; P, large pharmaceutical company; P_S, small pharmaceutical company; p, priority review; s, standard review; U, university. See BOX 1 for an explanation of the definitions. *These totals do not apply to the classification by scientific novelty of NMEs alone (the fourth section of the table). For these sections only, the total numbers in each category are P: 122.3, B: 20.2, U→P: 15.65, U→B: 24.85, all categories: 183. ‡Only 3.1 drugs are in these fields. The values mainly reflect sales of alemtuzumab (Campath, approved in 2001), interferon-β1a (Rebif, approved in 2002) and cetuximab (Erbitux, approved in 2004).

under $200 million). The factors underlying the high prices and sales for some NTBs are complex, and are not discussed here (see Supplementary information S4 (box), note 2). NTBs account for over 80% of the total sales of drugs discovered in biotechnology companies and about 50% of sales attributable to U→B drugs (TABLE 3).

Among all 252 drugs, the five with the highest MPY sales are NTBs: bevacizumab (Avastin, which was approved in 2004 and is used in various oncology indications), etanercept (Enbrel, which was approved in 1998 and is used for treating various autoimmune disorders), trastuzumab (Herceptin, which was approved in 1998 for breast cancer), infliximab (Remicade, which was approved in 1998 and is used for treating various autoimmune disorders) and adalimumab (Humira, which was approved in 2002 and is used for treating various autoimmune disorders). The first four of these (the four highest-selling) are either drugs discovered by biotechnology companies or U→B drugs. Each of these four had 2008 sales of over $5 billion (and an upward trend in sales), was scientifically novel and was probably approved on a priority basis.

Focusing only on NMEs reveals that drugs discovered by biotechnology companies and U→B NMEs tend to have substantially lower MPY sales than NMEs discovered by pharmaceutical companies (TABLE 2). However, as shown in TABLE 3, more of the total revenue from drugs discovered by pharmaceutical companies in the period studied is attributed to follow-ons or sNMEs than to scientifically novel drugs, pNMEs or NTBs, whereas the opposite is the case for drugs discovered by biotechnology companies and U→B drugs. Interestingly, when all polypeptide and polynucleotide drugs are classified as NTBs, the MPY sales of pNMEs discovered by biotechnology companies are close to that of pNMEs discovered by pharmaceutical companies (TABLE 2). This is because most of the polynucleotide and small polypeptide drugs that CDER approved as pNMEs were drugs discovered by biotechnology companies or U→B drugs that have had low sales. Therefore, removing these from the set of pNMEs increases MPY sales for the remaining pNMEs that were discovered by biotechnology companies.

Finally, MPY sales of U→P NMEs are generally much higher than those of U→B NMEs and even those of NMEs discovered by biotechnology companies. They are particularly high for U→P pNMEs (TABLE 2), although the majority of the U→P blockbusters that are responsible for this high average are not scientifically novel (see Supplementary information S2 (box), note 7). When classifying according to scientific novelty, MPY sales of scientifically novel U→P NMEs ($0.49 billion) are larger, but less substantially so, than those of novel U→B NMEs ($0.21 billion) and NMEs discovered by

Table 3 | **Total PYS (US$ millions) of 214 drugs approved from 1998 to 2005**

Type of drug (number of drugs)	Discovering organization				Total
	$P+P_S$ (125.4)*	B (36.94)*	U→($P+P_S$) (18.75)*	U→B (32.91)*	
Original CDER classification					
sNME (98)	69,826	1,581	2,455	1,779	75,641
pNME (85)	33,866	6,213	7,762	3,542	51,383
NTB (31)	2,943	37,290	3,777‡	5,189	49,199
As above, with NTBs expanded to include all polypeptide and polynucleotide drugs					
sNME (88)	63,749	897	2,432	836	67,914
pNME (73)	33,287	5,575	7,752	3,154	49,768
NTB expanded (53)	9,600	38,612	3,810	6,520	58,541
Classification by scientific novelty					
Follow-on (116)	72,857	13,470	9,403	3,076	98,805
Novel (98)	33,779	31,613	4,592	7,434	77,418
Classification by scientific novelty, NMEs only					
Follow-on NME (108)	70,284	2,487	7,838	1,940	82,549
Novel NME (75)	33,409	5,306	2,771	3,380	44,866
Overall					
Orphan drugs (44)	7,093	9,593	1,938	2,066	20,689
Total (214)*	106,636	45,084	13,994	10,509	176,223

B, biotechnology company; CDER, Center for Drug Evaluation and Research; FDA, Food and Drug Administration; NME, new molecular entity; NTB, new therapeutic biologic; P, large pharmaceutical company; P_S, small pharmaceutical company; p, priority (review); PYS, peak year sales; s, standard (review); U, university. See BOX 1 for an explanation of the definitions. *These totals do not apply to the classification by scientific novelty of NMEs alone (the fourth section of the table). For these sections only, the total numbers in each category are P: 122.3, B: 20.2, U→P: 15.65, U→B: 24.85, all categories: 183. ‡Only 3.1 drugs are in these fields. The values mainly reflect sales of alemtuzumab (Campath, approved in 2001), interferon-β1a (Rebif, approved in 2002) and cetuximab (Erbitux, approved in 2004).

biotechnology companies ($0.38 billion). This tendency for U→P drugs that generate high revenues to be NMEs that respond to unmet medical needs but are scientific follow-ons can be seen from TABLE 3, which shows that total sales of U→P pNMEs exceed sales of U→P sNMEs and NTBs combined, but sales of U→P follow-ons are more than twofold greater than sales of scientifically novel U→P drugs.

Sales trends for regions. FIGURES 4,5,6a show the sum of the peak-year sales (PYS) for the 214 drugs approved between 1998 and 2005 apportioned among countries and regions in a similar manner as FIGS 1,2,3a apportion the numbers of drugs (WDEs) approved between 1998 and 2007. The distributions in FIGS 4–6 are heavily influenced by blockbuster drugs.

FIGURE 4 shows the distribution of the total PYS for all 214 drugs according to region, with the distribution of the total WDEs of these drugs shown in brackets to aid comparison. Japan and Germany have total PYS values that are higher relative to their shares of WDEs, meaning that they tended to discover drugs with higher PYS than the world average. Most of the total PYS for the United States is attributable to drugs discovered by biotechnology companies or U→B drugs, whereas for all other regions except 'other', sales are dominated by drugs discovered by pharmaceutical companies.

Only in the United States, UK, Switzerland and Australia did the total PYS of scientifically novel drugs exceed the PYS of follow-on drugs (FIG. 5). Most of the PYS of scientifically novel US drugs are attributable to drugs discovered by biotechnology companies or U→B drugs, whereas such drugs make a negligible contribution to the PYS of scientifically novel drugs from most other countries (excluding Canada and Australia).

For sNMEs (FIG. 6), almost all sales, even of US drugs, are of drugs discovered by pharmaceutical companies. The PYS of sNMEs from Germany even exceed the PYS of US sNMEs, which are approximately the same as those from Japan.

With regard to pNMEs, only for the United States, the UK, Switzerland and Australia did the total PYS from pNMEs exceed those from sNMEs. Drugs discovered by biotechnology companies and U→B drugs made a notable contribution only to the PYS of pNMEs from the United States, Australia, Canada, Belgium and the Czech Republic, most of the Belgian and Czech pNMEs having been developed by US biotechnology companies. U→P drugs account for a notable proportion of the PYS of only US and Japanese pNMEs, although the Japanese U→P share is accounted for by only one drug, oxaliplatin (Eloxatin, which was approved in 2002) (see Supplementary information S3 (box), note 2). For other countries, drugs discovered by pharmaceutical companies account for most of the pNME PYS. Blockbusters influence the pNME PYS (particularly those of non-US pNMEs) to a greater extent than they influence sNME sales. The high pNME sales attributable to Japan and the UK are dependent almost entirely on three blockbusters each. However, pNME blockbusters from countries other than the United States, UK, Switzerland and Japan are rare (see Supplementary information S3 (box), note 8).

FIGURE 6 also shows that drugs discovered by US biotechnology companies and US U→B drugs dominated sales of NTBs. However, the PYS of NTBs discovered outside the United States are also mainly accounted for by drugs discovered by biotechnology companies and U→B drugs (mainly from the UK and Australia).

As discussed above, the majority of the PYS of drugs discovered by US biotechnology companies and US U→B drugs are attributable to NTBs. Repeating the scientifically novel versus follow-on analysis for NMEs alone yields PYS distributions (not shown) that are similar to those for sales of sNMEs and pNMEs in FIG. 6 (with the exception that the PYS of scientifically novel US and Japanese U→P NMEs are less than the PYS of U→P pNMEs from these two countries). Thus, the phenomenon noted at the end of the previous subsection, that high-revenue U→P pNMEs tend to be scientific follow-ons, is determined mainly by US pNMEs (which account for just under 60% of the PYS of U→P pNMEs).

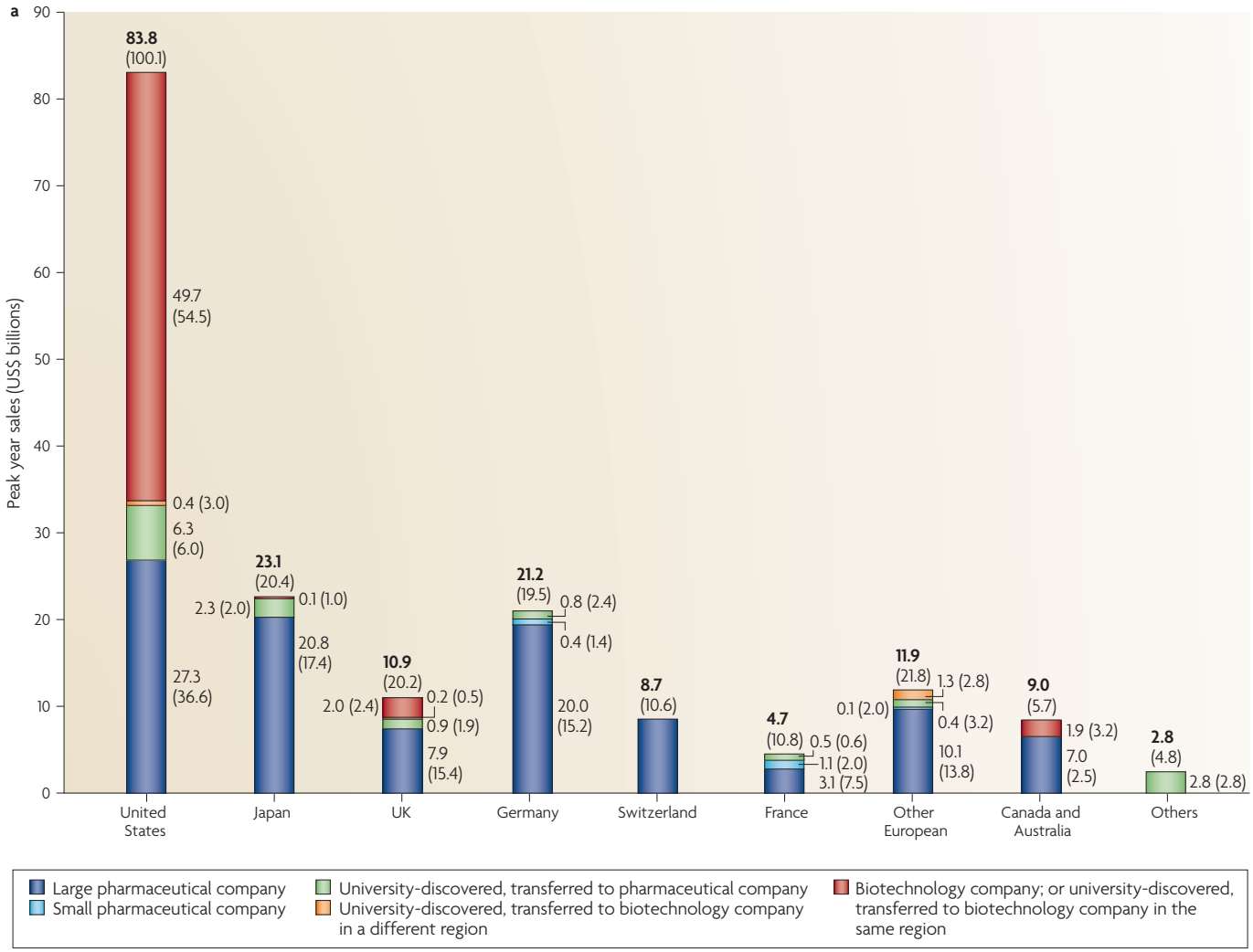

Figure 4 | **Allocation of total peak year sales of the 214 new drugs approved by the US Food and Drug Administration between 1998 and 2005.** The distribution of total peak year sales (PYS) for all 214 drugs according to region and type of discovering organization, as in FIG. 1. The distribution of the total whole drug equivalents (WDEs) for these 214 drugs is shown in brackets, with the total for each country or region at the top of each bar (beneath the total PYS for the country or region, in bold), and subtotals for the major types of discovering organizations also in brackets, adjacent to the PYS values for these discovering organizations. PYS in billions of current US$ are for the period ending in 2008; for details, see BOX 1 and Supplementary information S1 (box).

Orphan drugs

In 1983, the United States enacted legislation to encourage the development of drugs to treat orphan diseases, defined as conditions that affect fewer than 200,000 US citizens a year or conditions for which the cost of developing treatments cannot be covered by subsequent sales of these treatments in the United States. The key incentives are 7 years' exclusivity for the orphan indication in the US market (that is, the FDA will not approve an application by a different company to market the same drug for the same disease — an important protection because many orphan drugs are not covered by patents) and tax credits for up to 50% of the cost of clinical trials. Between 1983 and 2005, the FDA conferred orphan status on 282 drugs and biological products. By contrast, only about 10 drugs for rare diseases were approved by the FDA and brought to market in the decade before the enactment[7].

Of the 252 drugs in this study, 54 (21%) are approved by the FDA only for orphan indications (see Supplementary information S1 (box), note 9). Eighty percent of these received priority approval or are scientifically novel. Orphan drugs account for a substantial proportion (35%) of the scientifically novel and priority-approved drugs in the study. As indicated by the penultimate row of TABLE 1, they also account for over 40% of all university-discovered drugs, half of the university-discovered drugs developed initially by biotechnology companies, and over a quarter of those discovered in biotechnology companies themselves. Among innovative drugs in these categories, orphan drugs account for considerably higher proportions than those described above (see Supplementary information S3 (box), note 9). Sixty percent of the orphan drugs are attributable to US inventors (compared with 47% of all 252 drugs).

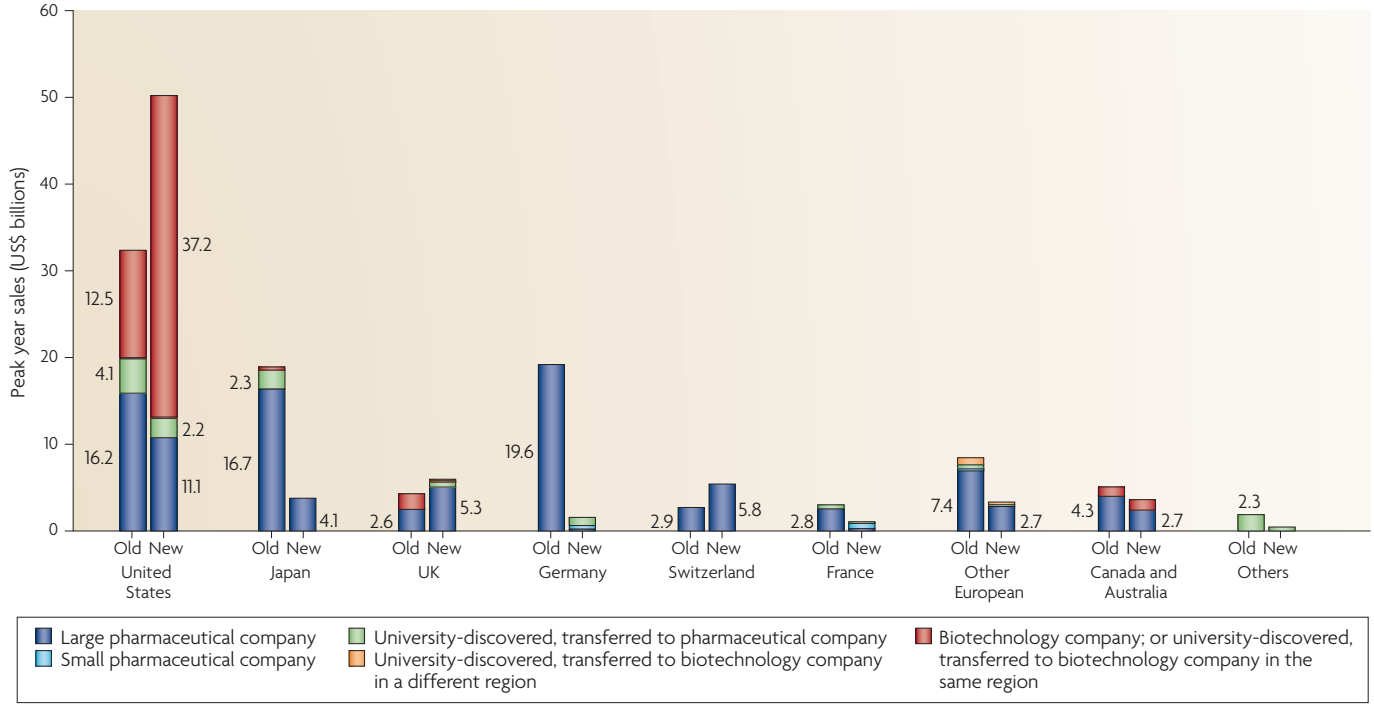

Figure 5 | **Distribution of the total peak years sales of drugs according to scientific novelty.** Applying the same distinctions as in FIG. 2, the total peak year sales (PYS) of scientifically novel drugs (new) are compared with follow-on products (old). PYS in billions of current US$ are for the period ending in 2008; for details, see BOX 1 and Supplementary information S1 (box).

Biotechnology companies are the major contributors to the discovery and development of orphan drugs. The penultimate row of TABLE 1 shows that over 20% of orphan drugs were discovered in biotechnology companies and ~35% were discovered in universities and developed initially by biotechnology companies. Almost all of these companies are based in the United States; US biotechnology companies were the initial developers of 80% of orphan drugs discovered at US universities and over half of those from non-US universities (see Supplementary information S3 (box), note 10).

The penultimate row of TABLE 2 shows that MPY sales of orphan drugs are only ~60% of that for the entire set of drugs. MPY sales of U→B orphan drugs are particularly low, contributing to the low overall mean values for U→B drugs. The higher mean for U→P orphan drug sales in part reflects the contributions of UK and US academics to, respectively, the discovery of the blockbusters temozolomide (Temodar, which was approved in 1999) and imatinib (Gleevec, which was approved in 2001). With only one or two other exceptions, small or regional pharmaceutical companies were the initial developers of U→P orphan drugs, and most of these companies later transferred these drugs to biotechnology companies for FDA approval and marketing (see Supplementary information S3 (box), note 11). So, except in rare cases of orphan drugs that promised substantial sales, later development of most U→P orphan drugs in the period studied was conducted by biotechnology companies and small pharmaceutical companies.

Apart from temozolomide and imatinib, the orphan drugs that have achieved blockbuster sales are trastuzumab, lenalidomide (Revlimid, which was approved in 2005), bortezomib (Velcade, which was approved in 2003) and bosentan (Tracleer, which was approved in 2001). The first three were primarily discovered by US biotechnology companies and the fourth was discovered by Roche's Swiss laboratories (although it is now marketed by a biotechnology company, Actelion). With the exception of bosentan for the treatment of pulmonary hypertension, these blockbuster orphan drugs are for cancer indications (in some cases, approvals in several indications have been achieved).

Japan and the European Union enacted orphan drug legislation in 1993 and 2000, respectively (see Supplementary information S4 (box), note 3). In total, the European Commission approved 44 therapeutic drugs for orphan indications from 2001 (the year it began to issue such approvals) to 2007 (see Supplementary information S4 (box), note 4). About 60% are attributable to US inventors, the same overall proportion as for the FDA-approved orphan drugs. European pharmaceutical companies have discovered and developed seven compounds that are approved as orphan drugs in Europe, all of which the FDA has also approved as orphan drugs. Five of these are from Swiss pharmaceutical companies. Also, three compounds developed by European biotechnology companies or small pharmaceutical companies have been approved as orphan drugs in Europe, and so far two have been approved in the United States. Almost all of the orphan drugs discovered by European

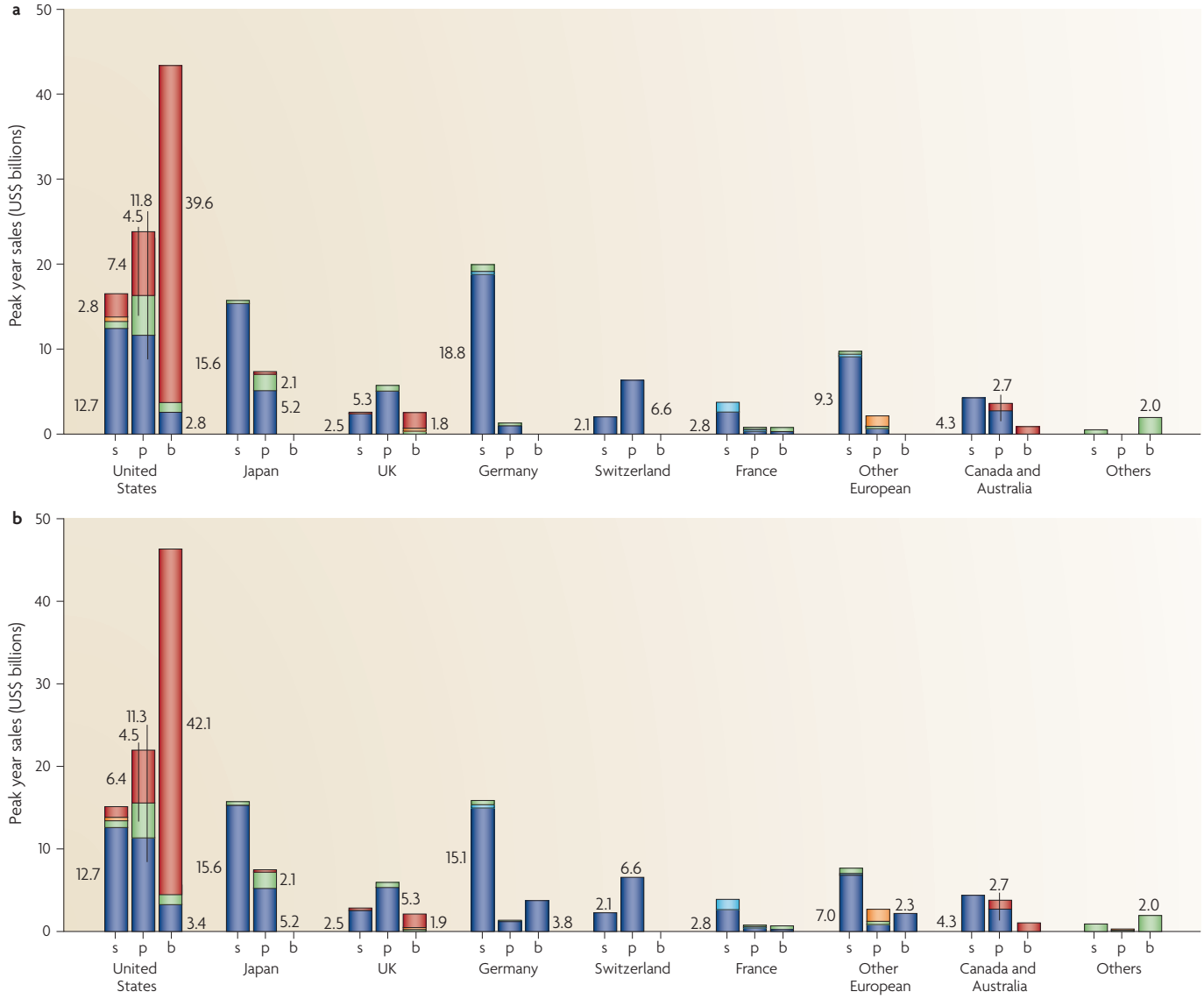

Figure 6 | **Distribution of the total peak years sales of drugs according to regulatory review priority.** Applying the same distinctions as in FIG. 3, the distribution of the total peak year sales (PYS) of standard new molecular entities (s), priority-approved new molecular entities (p) and new therapeutic biologics (b) is shown in part **a**, with the expanded definition for new therapeutic biologics used in part **b**. PYS in billions of current US$ are for the period ending in 2008; for details, see BOX 1 and Supplementary information S1 (box).

pharmaceutical companies were first approved in the United States, whereas the orphan drugs developed by biotechnology companies or small pharmaceutical companies were first approved in Europe (see Supplementary information S3 (box), note 12).

Japan has produced few orphan drugs. Between 1998 and 2007, Japan approved 58 drugs for orphan indications only (see Supplementary information S4 (box), note 4). Most of these were discovered outside Japan, and many are not designated as orphan drugs in other markets or recently approved there. Only four Japanese orphan drugs were discovered in Japan, and none of these has been approved in the United States or Europe (see Supplementary information S3 (box), note 13). These findings suggest that the European legislation, but so far not the Japanese legislation, has encouraged domestic discovery and development of orphan drugs. Moreover, the European legislation may have had its greatest impact in achieving this goal through biotechnology companies, as was the case for the US legislation.

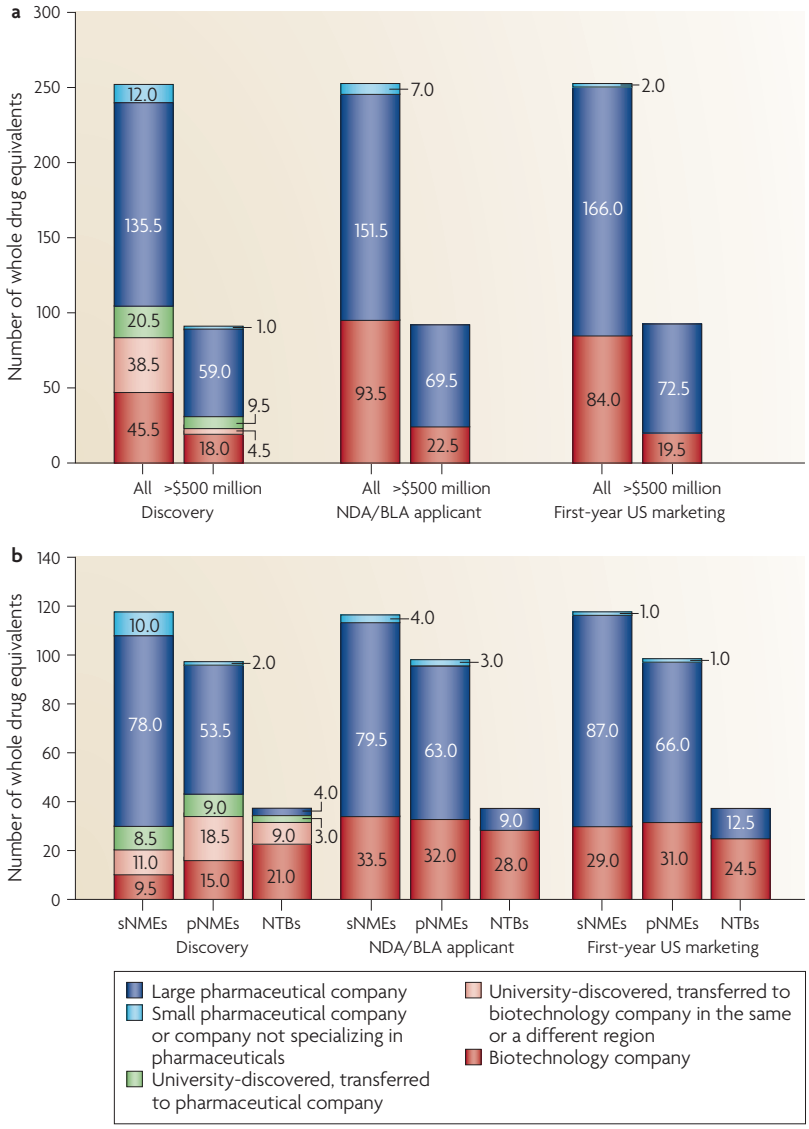

Figure 7 | **Organizations undertaking discovery and development of new drugs at key stages. a** | Distribution of the types of organizations responsible for discovery and development at key stages for all drugs and for those with peak year sales above US$500 million from 1998 to 2008. **b** | The same comparison for standard new molecular entities (sNMEs), priority-approved new molecular entities (pNMEs) and new therapeutic biologics (NTBs). For details, see BOX 1 and Supplementary information S1 (box), note 10.

Downstream development

What is the role of biotechnology companies beyond discovery and early development? To investigate this question, the subset of 86 new drugs for which the overall discovery and development is at least half attributable to biotechnology companies or to universities that transferred to biotechnology companies was analysed. The discovering biotechnology companies (or the companies to which the drugs were initially transferred from the discovering universities) themselves filed the new drug application (NDA) for 51 (60%) of these. The remaining 40% were divided approximately evenly between drugs that were taken through to FDA approval by another biotechnology company or by a pharmaceutical company. Pharmaceutical companies were the sole principal marketers for the first year of US sales of one-quarter of these 86 drugs, whereas two-thirds were marketed in the United States only by biotechnology companies during the first year of sales.

Among the 51 drugs taken by a single biotechnology company from discovery to NDA, six were licensed to another biotechnology company for marketing in the United States, six were licensed to pharmaceutical companies for marketing, and the other 39 (45% of the subset of 86 drugs) were taken from discovery through at least the first year or marketing or co-marketing in the United States by the single biotechnology company. This phenomenon was most common in the case of the largest and most mature biotechnology companies — Genentech, Amgen, Genzyme and Biogen (see Supplementary information S3 (box), note 14) — and in the case of orphan drugs (16 out of 32 orphan drugs discovered by biotechnology companies or U→B orphan drugs). This is not surprising given the resources of the largest biotechnology companies and the tendency for some biotechnology companies, such as Genzyme, to focus on orphan drug indications. Nevertheless, small or mid-size biotechnology companies took 15 non-orphan drugs all the way from discovery through to initial marketing (see Supplementary information S3 (box), note 15).

Genentech, Amgen, Genzyme and Biogen had greatest impact on the group of 37 NTBs, accounting for the discovery of 25%, the FDA applications for 40% and the first-year US marketing for 40% of these products. Nevertheless, smaller biotechnology companies discovered over 60% (or partnered with discovering universities), filed the regulatory applications for 35% and marketed 30% for at least the first year in the United States.

In addition to their role in the development of the 86 drugs discussed above, biotechnology companies were the regulatory applicants for 26 drugs that were discovered by pharmaceutical companies or U→P drugs. The number of these drugs, which the pharmaceutical companies out-licensed rather than developing them themselves, exceeds that of the 17 drugs discovered by biotechnology companies or U→B drugs that pharmaceutical companies submitted for FDA approval. Their MPY sales were $440 million, about half the mean for all drugs in this study (TABLE 2). Although this indicates a tendency for drugs with low sales potential to be transferred from pharmaceutical companies to biotechnology companies that are willing to take them through the later stages of development, the important roles of DebioPharm and Imclone in the clinical development of oxaliplatin (Eloxatin, a pNME that was approved in 2002) and cetuximab (Erbitux, a NTB that was approved in 2004), respectively, are examples of biotechnology companies picking up the development of future blockbusters from established companies.

FIGURE 7a compares the types of organizations responsible for discovery and development at key stages for all drugs with those for drugs that had PYS above $500 million from 1998 to 2008. The overall proportion of drugs being developed by biotechnology companies relative to that from pharmaceutical companies did not

vary greatly at the various stages of the process, although a larger proportion of drugs with high MPY sales are discovered and developed by pharmaceutical companies than those with low MPY sales.

Analysing the development process separately for sNMEs and pNMEs (FIG. 7b) shows that the proportions of sNMEs for which only the later development was sponsored by biotechnology companies is higher than the proportion discovered by biotechnology companies. This is primarily due to biotechnology companies in-licensing sNMEs that are discovered by pharmaceutical companies and have low-revenue prospects before NDA filing. The proportion of pNMEs managed by biotechnology companies remains fairly constant throughout the process, although this masks a substantial amount of licensing of pNMEs discovered by biotechnology companies and U→B pNMEs to pharmaceutical companies and vice versa before NDA filing. The case is similar for scientifically novel drugs (data not shown).

One other noteworthy point is that the early development of scientifically novel university drugs by major multinational pharmaceutical companies was rare during the period studied. Exceptions include the pNMEs temozolomide (which was approved in 1999), imatinib (which was approved in 2001) and fondaparinux (Arixtra, which was approved in 2001). Such drugs were discovered through direct collaboration between academic and pharmaceutical-company scientists (see Supplementary information S3 (box), notes 1, 2 and 16). Biotechnology companies licensed twice as many NMEs from universities as did pharmaceutical companies, and two-thirds of these were scientifically novel. The MPY sales for these drugs were small compared to the U→P NMEs (TABLE 2) but, because of larger numbers of scientifically novel U→B NMEs, their total sales exceed those of novel U→P NMEs (TABLE 3).

In summary, biotechnology companies were active at all development stages for all categories of drugs. Most drugs discovered by biotechnology companies and U→B drugs were developed through to initial marketing by biotechnology companies. The oldest and largest of the biotechnology companies carried out an important, but not an overwhelming, share of this development. When considering pNMEs, the contribution of biotechnology companies relative to pharmaceutical companies was greatest at the discovery and initial development stages, and biotechnology companies were the main contributors at all stages of the development of NTBs.

Concluding observations

A major aim of this study is to help understand factors that could promote the discovery of scientifically and/or medically innovative drugs. In this respect, a key finding is that biotechnology companies and universities that transfer their discoveries to such companies accounted for approximately half of the FDA-approved drugs that were scientifically innovative and half of those that respond to unmet medical needs in the period 1998–2007 (TABLE 1). Their contribution to the development of follow-on drugs was considerably smaller. Most of these biotechnology companies were located in the United States. Outside the United States, the sales data suggest that most of the established pharmaceutical companies concentrated their discovery and development efforts on lower-risk drugs; for example, those with proven mechanisms of action. In summary, without the contribution of biotechnology companies, the number of new innovative drugs discovered in this period that respond to unmet medical needs would have been substantially lower, particularly for orphan drugs, NTBs and university-discovered compounds.

The factors that have promoted a favourable environment for research ultimately leading to innovative drugs in the United States are complex and are not discussed comprehensively here. However, one important probable underlying factor is the levels of public funding for academic biomedical research. US government support for such research, primarily provided through the National Institutes of Health (NIH), has typically constituted a substantially higher percentage of the gross domestic product than equivalent funding levels by other governments: over twice the percentages for Japan and major continental European countries (see Supplementary information S4 (box), note 5). The results of open, publicly supported academic research are valuable for both biotechnology and pharmaceutical companies, as are the scientists trained in the course of academic research.

A related factor could be the system of allocating government support for academic research. The NIH system for peer review has been criticized for awarding too little funding to younger researchers and to non-traditional projects, especially in times of flat funding and declining grant application success rates. Nevertheless, it probably focuses a greater degree of thought and deliberation by experts on competing proposals than does, for example, the allocation system for most Japanese government research and development programmes. The Japanese programmes tend to make awards to consortia of scientists (and sometimes also companies) that are controlled by senior professors. Even in the case of awards to individual scientists, the review process is less rigorous than that for NIH grants. Combined with other factors such as the monopoly full professors have on most laboratory space and a recruitment and promotion system that remains patronage-based, this makes it more challenging for young Japanese researchers to establish themselves independently and to pursue novel, high-quality research projects[8–11].

Another likely factor is career flexibility for biomedical researchers and generally favourable social attitudes towards changing jobs and working in new companies in the United States (see Supplementary information S4 (box), note 6). By contrast, scientific career options for Japanese biomedical Ph.D. graduates, for example, are limited mainly to academia and pharmaceutical companies, and job changes by Japanese corporate researchers are rare except towards the end of their careers. This absence of professional mobility not only restricts personal networks and the cross-fertilization of ideas and initiatives, but also limits opportunities for researchers to find work that is most suited to their interests and where they can be most productive[11–14].

Nevertheless, in addition to the probable role of government funding for biomedical research and professional mobility, it is clear that the biotechnology companies themselves in the United States have played a key part in its innovative drug output in the period studied, which has not yet been mirrored elsewhere, except on a smaller scale in Canada and Australia. Factors (not necessarily unique to the United States) that might underlie the innovative strength of new companies include:

- The organizational culture in a company has important effects on the potential for innovation. It is often considered that biotechnology companies are more likely to provide a conducive environment for entrepreneurship than large, established pharmaceutical companies — an idea that seems to be supported by studies in the information technology industry[13,14]. For example, characteristics particular to an entrepreneurial environment probably motivate managers and researchers at biotechnology companies to work concertedly on their lead compounds. By contrast, the decision-making process in even the most well-managed large organizations may reflect a tendency to focus on products and research methods that have proven successful, and increase the likelihood that new discoveries will be overlooked or their development abandoned. This phenomenon has been documented in the information technology and pharmaceutical industries[15,16], and the histories of oxaliplatin and alemtuzumab (Campath) in this study provide some illustration (see Supplementary information S3 (box), note 2). In addition, the bureaucracy that is characteristic of large organizations can be detrimental to research, as discussed recently by the former Chief Executive Officer of GlaxoSmithKline (GSK)[17].
- New companies can attract and retain talented researchers. Surveys have suggested that the most well-trained biomedical Ph.D. graduates are often drawn to biotechnology companies rather than pharmaceutical companies and that employee job satisfaction is greater in biotechnology companies (see Supplementary information S4 (box), note 7).

However, a supportive environment for entrepreneurship is necessary for these advantages to come into play. Some characteristics of such an environment that may be particularly relevant to the US situation, at least until recently, are:

- Relatively plentiful venture capital and other forms of financing compared with other regions.
- Open immigration policies[18].
- The Bayh–Dole amendments that facilitated the exclusive licensing of government-funded university inventions (see Supplementary information S4 (box), note 8). Exclusive licences to university discoveries, university technology transfer management that has generally been supportive of start-ups, and close relationships with universities have been important for the formation of biotechnology companies and have aided the development of many biotechnology products (see Supplementary information S4 (box), note 9).
- An open innovation stance on the part of large pharmaceutical companies under which they regard biotechnology companies as major sources of new drugs and drug discovery technologies.
- As mentioned above, high labour mobility and favourable attitudes towards changing jobs and working in new companies[13,14].

Time will tell whether the environment for biotechnology companies will improve outside the United States. For example, the Japanese government has implemented various measures to improve this environment in Japan. Among the most important are allowing academics to be engaged in start-ups, the establishment of concessionary sections of the main stock exchanges that facilitate the listing of biotechnology stocks, and various mechanisms to provide financing for biotechnology companies. Whether these are sufficient to overcome the barriers to science-based entrepreneurship is an open question. Japan does not score highly on all the characteristics of a supportive environment for entrepreneurship listed above (except that university discoveries can now be exclusively licensed to biotechnology companies), nor on government support for biomedical research and its method of allocation[8–11] (see Supplementary information S4 (box), note 5). Nevertheless, by mid-2010, 22 independent Japanese biotechnology companies had at least 34 Japan-discovered drugs on the market in Japan (three products) or in clinical trials. By contrast, before 2004, therapies from probably only three Japanese biotechnology companies (approximately five therapies in total) were approved or in clinical trials (see Supplementary information S4 (box), note 10).

The findings of this study regarding the relative success of biotechnology companies in discovering innovative drugs, and in taking on the early development of innovative drugs discovered in universities, could also provide insight into recent strategic trends for large pharmaceutical companies. First, some companies, such as GSK[17], are trying to make their organizations less bureaucratic and more science-driven. Second, some large pharmaceutical companies are now devoting more resources to drugs that target rare diseases or specific patient populations[19], which may be reflected in the recent approvals of innovative drugs from such companies that are not for typical blockbuster indications (see Supplementary information S3 (box), note 17). Third, discovery-oriented collaborations between pharmaceutical companies and academic institutions are emphasizing closer cooperation between pharmaceutical-company and academic scientists than was previously the case[20,21]. Such closer cooperation might result in pharmaceutical companies pursuing the development of a greater number of drugs with novel mechanisms of action. However, it remains to be seen whether there will be a change in the tendency that was seen in the period studied for pharmaceutical company–university collaborations outside the United States and the UK to focus on less innovative drugs (see Supplementary information S3 (box), note 18).

Questions could be raised about the efficiency of relying on independent biotechnology companies for innovative drug discovery (see Supplementary information S4 (box), note 11). Nevertheless, the findings of this study, the frequent acquisitions of biotechnology companies by pharmaceutical companies, and the prominence of drugs derived from these companies in the pipelines of pharmaceutical companies[22] all suggest that major pharmaceutical companies have decided that it makes business and scientific sense to let universities, biotechnology companies and investors in such companies assume much of the greater risk associated with discovering highly innovative drugs and bringing them to the proof-of-concept stage. However, the future of biotechnology companies as sources of innovative drugs should not be taken for granted. Diminished early-stage venture capital for new companies, poor prospects for initial public offerings, diminished immigration of scientists and science students into the United States, and moves towards patent 'reform' in the United States that may undermine intellectual-property protection for new science-based companies all raise questions about the future of this 'US model' of innovation that, at least in pharmaceuticals, relies so much on new companies. In the interest of public health and to ensure public benefits from publicly funded biomedical research, all countries should improve their environments for science-based entrepreneurship.

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Competing interests statement

The author declares competing financial interests: see web version for details.

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