

Box S3 | Notes on the attribution, classification or characteristics of particular drugs or groups of drugs

Note 1. The following cases discuss four drugs for which the attribution of contributions to their discovery was based to a significant extent on information besides patents, even though patents cover the compounds or the key synthetic methods:

• *Case 1: Gleevec.* Only one US patent (5521184) covering the anticancer drug Gleevec (2001, pNME) is listed in the FDA Administrative Correspondence. This patent indicates the compound was invented by researchers in Ciba-Geigy's Swiss laboratories. This is confirmed by Vasella's 2003 history of the drug¹. However, Brian Druker, first as a physician-researcher at Dana Farber Cancer Institute and then as a faculty member at Oregon Health Sciences University, worked closely with Ciba-Geigy researchers in the discovery and development of Gleevec. He elucidated the role of the abnormal protein that causes most cases of chronic myeloid leukaemia. He suggested that Ciba researchers target this protein, he developed assays to determine whether the prototype drugs were having the predicted, desired biochemical effect, and he encouraged Ciba-Geigy and later Novartis to move forward with clinical trials^{1,2}. Taking these factors into account, but also adhering to the basic methodology of this paper to place greatest weight on the inventors of the active compounds, discovery was allocated 75% to the Ciba-Geigy researchers and 25% to Druker (university transferring to pharmaceutical company).

• *Case 2: Prezista.* US patents 5968942 and 6248775 B1 describe the structure of the second generation HIV protease inhibitor Prezista (2006 pNME). These and a large number of other patents issued to Searle, as well as scientific publications by Searle researchers, indicate that in the early 1990s, Searle's St. Louis laboratory had one of the leading teams of scientists focused on the discovery of HIV protease inhibitors. Among the over 200 compounds claimed as HIV protease inhibitors in US 5968942, Searle developed several in the 1990s. However, Searle probably did not realize the potential of the compound that became Prezista to overcome some of the resistance problems that plagued the first-generation HIV protease inhibitors. In the late 1990s, Searle licensed many of its HIV protease inhibitors patents to Tibotec, a Belgian biotechnology company founded in 1994 by researchers from Janssen and Catholic University of Leuven. Tibotec's strategy for discovering HIV drugs included finding and cloning as many resistant variants of HIV protease and reverse transcriptase as possible. Academic researchers at NIH, University of Illinois at Chicago and Johns Hopkins (some of whom had been researchers in major pharmaceutical companies such as Merck and Abbott) were using crystallography and other molecular modelling techniques to identify structures that would overcome the resistance problem. Their work probably helped Tibotec to identify lead development candidates, including the compound that became Prezista (see REFS 3-5, PCT application no. PCT/US99/14119 and US patent application pub. no. US2005/0158713 A1). Taking all these factors into account, Prezista was attributed half to Searle (and other US pharmaceutical companies whose research helped guide the identification of Prezista), one quarter to Tibotec, and one quarter to US academic institutions whose discoveries were transferred to an out-of-region biotechnology company.

• *Case 3: Kuvan.* Kuvan (2007 pNME), is a synthetic version of the natural co-factor tetrahydrobiopterin to treat tetrahydrobiopterin-responsive phenylketonuria. Because Seymour Kaufman at the National Institute of Mental Health of NIH was primarily responsible for showing the physiologic and clinical significance of tetrahydrobiopterin, the discovery was attributed 70 percent to him. The actual synthetic method is claimed in patents (US 4713454 and Jpn 1996-164213) assigned to Shiratori and Suntory (companies classified as P_s and P*, respectively) by the employee inventors. However, a similar if not identical method was described by Nagoya University researchers in REF. 6 nine months *before* the filing of the Japanese patent applications (60-12477 & 60-12478) on which the priority of US and Japanese patents is based (although neither the Japanese nor US patents assigned to Shiratori and Suntory refer to the Nagoya University researchers or their work). Thus the synthetic method was credited to Nagoya University and 30 percent of the discovery attributed to the Nagoya

University researchers. All of the above academic discoveries were considered to have been transferred to pharmaceutical companies (Shiratori and Suntory in equal measure).

• *Case 4: Refludan.* Refludan (lepirudin, 1998 pNME) is a recombinant form of hirudin, which is found in the salivary glands of leeches and is an inhibitor of thrombin. In the US, Refudan is approved as an anticoagulant in patients who are sensitive to heparin, especially those at risk of thrombo-embolism or re-occlusion following vascular procedures. Academic research, particularly that by Fritz Markwardt at the Medical Academy of Erfurt and other European academics, showed hirudin's clinical potential. They also demonstrated the feasibility of making recombinant hirudin, and the antithrombotic efficacy of the recombinant version in laboratory mammals, before the priority date of the Hoechst patent⁷. Hoechst claims lepirudin on the basis of a brief 8-page patent (US 5180668) issued in 1993 whose priority extends back to a German application in 1988. The rather modest number of pre-1993 scientific publications by Hoechst researchers that deal with hirudins often have academic co-authors (for example, REF. 8) or are published in a journal edited by Markwardt (for example, REF. 9). Thus it seems likely that German academics played a significant, direct role in the discovery and development of the recombinant version of hirudin that became Refludan. The discovery was therefore attributed half to Hoechst and half to German universities.

Note 2. The following four cases illustrate application of the criterion that the first transferee must have taken significant steps to develop the drug, even though it might have ultimately given up:

• *Case 1: Eloxatin.* Eloxatin (2002 pNME) was discovered by Professor Kidani of Nagoya City University about 1976 (US patent 4169846). Researchers at Tanaka Precious Metals (TPM, Tanaka Kikinzoku) spent several years to develop more stable versions of the drug and better production methods (see US patents 5290961, 5338874 and 5420319), and thus TPM was considered to be the initial transferee (U→P*). However, neither Kidani nor TPM could find a company that would sponsor clinical trials. TPM transferred its rights to a Swiss biotechnology company, DebioPharm, which concluded a 1994 license agreement with Sanofi but continued clinical trials, obtaining initial marketing approval in France in 1996. Sanofi also undertook clinical trials and was the FDA NDA applicant. However, Eloxatin is classified as a U→P drug, not because of Sanofi's clinical development, but because of TPM's preclinical work.

• *Case 2: Campath.* Similarly, Campath (one of the first humanized monoclonal antibodies, which was approved in 2001 for chronic lymphocytic leukaemia and is now in Phase III trials for multiple sclerosis) was discovered by Cambridge University researchers who initially partnered with a subsidiary of the Wellcome Foundation (the UK branch of Burroughs Wellcome). Although Wellcome abandoned development and the clinical trials were continued first by Leukocyte (a Massachusetts biotechnology company) and then by Millennium and ILEX (also US biotechnology companies), Campath is classified as a U>P drug. (<http://users.path.ox.ac.uk/~scobbold/tig/CAMPATH/CAMPHIST.HTM> and <http://www.research-horizons.cam.ac.uk/features/-p-campath--p-.aspx>)

• *Case 3: Zavesca.* Zavesca (sNME approved 2003 for adult Gaucher's disease) is a more difficult case. Both the key patent filed in 1993 and a scientific article published the same year make clear that its ability to inhibit glycolipid synthesis was jointly discovered by three researchers at Oxford University and one at Monsanto-Searle in Missouri. Searle had been interested in the Zavesca family of compounds as HIV drugs, but clinical trials published in 1995 raised safety concerns and Monsanto-Searle abandoned development of these compounds, although their ability to treat rare genetic glycolipid storage diseases was becoming apparent. In 1998, Seale licensed Zavesca to the UK biotech, Oxford GlycoSciences (OGS), which in 2002 licensed rights to the Swiss biotechnology company Actelion, which went on to obtain FDA approval and market the drug. Whether Searle made any substantial steps towards commercializing Zavesca for Gaucher's disease is not clear. The author

searched for articles describing research in the mid and late 1990s related to Zavesca and glycolipid storage diseases, and found several by Oxford and OGS researchers but none by Searle scientists. Thus the locus of early development work was assumed to have passed primarily from Oxford to OGS. Since Bayer scientists probably discovered the active compound (claiming it in a broad patent, US 4639436, that did not indicate its utility for glycolipid storage diseases) origins were attributed 20% to Bayer, 20% to Searle and 60% to Oxford University transferring to a same region biotechnology company ($U \rightarrow B_{in}$).

• *Case 4: Vidaza.* Similarly, although the DNA methylation inhibitor and leukaemia drug, Vidaza (2004 pNME), was licensed first to Pharmacia, there is little evidence that Pharmacia committed substantial resources towards development. Indeed, many of the early clinical trials were funded by NIH (Glover AB & Leyland-Jones B, 1987, Biochemistry of azacitidine: a review, Cancer Treatment Reports 71: 959-964). Thus, the US biotechnology company Pharmion, which licensed the compound from Pharmacia in 2001 and took it through clinical trials and into marketing, was considered the first transferee.

In contrast to Zavesca and Vidaza, it appears that Zeneca Agrochemicals and Mitsui Norin were actively involved in the initial development of Orfadin (2002 pNME) and Veregen (2006 sNME), respectively, so the university contributions to the discoveries of these two drugs were considered to have been initially transferred to pharmaceutical companies, even though the NDA applications were filed by biotechnology companies.

Note 3. The scientifically novel drugs whose discovery is at least 20% attributable to small pharmaceutical companies (P_s) are: Provigil (1998 sNME from Lab. L. Lafon, FR), Namenda* (2003 sNME from Merz, GE) and Campral (2004 pNME from Meram/Cooper, FR), while the follow-on drugs are at least 20% attributable to small pharmaceutical companies: Precedex (1999, sNME from Farnos, Finland), Sanctura (2004, sNME from Dr. R Pflieger, GE), Xifaxan (2004 sNME from Alpha Wassermann, IT) and Omnaris (2006 sNME from Elmu, SP). The first five of these act either on the central or peripheral nervous system.

The following predominantly non-pharmaceutical companies (P^*) contributed at least 20% to the discovery of scientifically novel drugs.

- Merz (Namenda* 2003 sNME);
- Stauffer Chemicals (Orfadin* 2002 pNME);
- Mitsui Norin (Veregen* 2006 sNME);

while the following discovered or initially developed follow-on drugs:

- Snowbrand (Evoxac 1999 sNME);
- Aginomoto (Starlix* 2000 sNME);
- Meiji Seika (Spectracef 2001 sNME);
- Murrer & Powell (Fosrenol 2004 sNME);
- Norsk Hydro (Omacor* 2004 sNME);
- Givaudan (Anthelios SX 2006 sNME).

Merz is included in both lists because it was probably a small cosmetics-oriented company when it began working on memantine (Namenda) for CNS diseases in the early 1970s. In the course of developing memantine, Merz grew into an R&D-based pharmaceutical company, and in the main analysis it is classified as a small pharmaceutical company (P_s). The above lists indicate that drug discovery by small pharmaceutical companies is primarily a phenomenon of Continental Europe, while discovery by established companies whose main business is not pharmaceuticals is, in large part, a phenomenon of Japan.

Not included in either of the above lists are two priority approved NMEs that were discovered in universities but whose initial development was undertaken by established Japanese companies whose main business is not pharmaceuticals: oxaliplatin (Eloxatin, 2002,

from Nagoya City University, initially developed by Tanaka Precious Metals) and sapropterin (Kuvan, 2007, from NIH and Nagoya University). Kuvan is a scientifically novel drug that was initially developed by Suntory in collaboration with the small Japanese pharmaceutical company, Shiritori.

In both lists, * indicates drugs that probably were discovered through collaboration with universities, based upon the existence of key patents that list inventors from both universities and companies. The finding that at least half of the P* drugs probably arose from collaborations with universities; along with the development histories of Namenda, Veregen, Eloxatin and Kuvan; suggest that collaboration with universities can help established companies move into drug discovery from other business areas, and that these companies can also play important roles in the early development of innovative university drugs.

Note 4. The following lists all non-US B and U→B drugs by country:

- *Canada:* DUSA (Toronto) developed Levulan Kerastick (1999, sNME, phototherapy for actinic keratoses) from Queens University, Ontario. QLT PhotoTherapeutics (Vancouver) developed Vizudyne (2000, pNME, phototherapy for macular degeneration) from the University of British Columbia.

- *Australia:* Biota (Melbourne) initially developed Relenza (1999, pNME for influenza) from Monash University. Transkaryotic Therapies of Cambridge, Massachusetts initially developed Elaprase (2006 NTB for Hunter's disease) from Adelaide Children's Hospital (ACH). ACH researchers also played a role in the discovery of Myozyme for Pompe's disease, which was developed through to marketing by Genzyme. Peptech's tumour necrosis factor monoclonal antibody technology is probably incorporated in Humira (2002 NTB for RA, see case study in Box 1, note 4).

- *United Kingdom:* Bioxex invented Colazal (2000 sNME for ulcerative colitis). Oxford GlycoSciences carried out the early development of Zavesca (2003 sNME for Gaucher's disease). Britannia Pharmaceuticals undertook initial development of Apokyn (2004 pNME for Parkinson's). A portion of Humira's discovery (2002 NTB see Box 1, note 4) is attributable to Cambridge Antibody Technology. Celltech played a major role in humanizing the CD33 monoclonal antibody that Lederle integrated with the anticancer drug, ozogamicin, to create Mylotarg (2000 pNME see Box 1, note 4). Scotgen played a small role in the discovery and early development of Tysabri (2004 NTB for multiple sclerosis).

- *Japan:* RTech Ueno in Osaka discovered both Rescula (2000 pNME for glaucoma) and Amitza (2006 sNME for constipation).

- *Israel:* Teva and academic researchers at Technion jointly discovered Azilect (2006, sNME for Parkinson's disease) which Teva went on to commercialize. This accounts for nearly 30 percent of Israel's 3.7 drugs, so Israel might also be considered a country where biotechnology companies account for a significant proportion of drug discovery.

- *Belgium:* A portion of the discovery of the second-generation HIV protease inhibitor, Prezista (2006, pNME) is attributable to the Belgian biotechnology company, Tibotec. (See note 1 above.)

All of Australia's 2.3 drugs arose in universities or biotechnology companies, or in universities that partnered with biotechnology companies (although some of these biotechnology companies are US, not Australian), and, except for Humira, are scientifically novel pNMEs or NTBs. Two of Canada's 4.5 drugs were discovered in universities and developed through initial marketing by Canadian biotechnology companies (see previous note.) One of Israel's 3.7 drugs was jointly discovered by Israeli biotech and university researchers. The others were all discovered in Israeli universities and transferred to pharmaceutical companies.

Note 5. The following lists, by country, all drugs attributed at least 20% to universities outside of the United States, Canada or Australia. Canadian and Australian university drugs were all transferred to biotechnology companies and thus are listed in Note 4 above. (*indicates scientifically novel drugs).

Other countries where university discoveries account for over 20 percent of new drugs:

- Most Swedish university drugs were transferred to pharmaceutical companies; see supplementary information S2 (table) for Curosurf (1999 sNME), INOmax* (1999 pNME), and Orfadin* (2002 pNME.) In the case of Orfadin, the Swedish university researchers worked initially with Zeneca Agrochemicals. Also the majority of Israeli university drugs were transferred to pharmaceutical companies; see Exelon (2000 sNME), Evoxac (2000 sNME), Rebif (2002 sNTB), Erbitux* (2004 pNTB) and Azilect (2006 sNME).
- US biotechnology companies were the developers (even through initial marketing) of all university drugs from the Czech Republic. See Viread (2001 pNME), Hepsera (2002 pNME), Vidaza* (2004 pNME), Dacogen* (2006 sNME) and Tyzeka (2006 sNME).
- US biotechnology companies were also the initial developers of all university drugs from the Netherlands; see Myozyme* (2006 pNTB) and Neupro (2007 sNME).
- One of the Chinese drugs, Trisenox* (2000 pNME), was developed to marketing by a US biotechnology company while the other, Veregen* (2006 sNME), was developed initially by the pharmaceutical unit of a Japanese agricultural trading company.

Countries with a mature pharmaceutical industry, where universities generally account for 10 to 15 percent of drug discovery:

- Japan's university discoveries were transferred exclusively to pharmaceutical companies; see Acova (2000 sNME), Starlix (2000 sNME), Eloxatin (2002 sNME) and Kuvan* (2007 pNME).
- Most of Germany's university drugs were also transferred to pharmaceutical companies; see Recludan (1998 pNME), Ferrlecit* (1999 pNME), Reminyl* (2001 sNME) and Namenda* (2003 sNME). However, Sucraid* (1998 pNME) was developed through to initial marketing by Orphan Medical, a US biotechnology company.
- A majority of UK university drugs were developed, at least initially, by domestic and US biotechnology companies; see Zavesca* (2003 sNME), Apokyn* (2004 pNME), Tysabri* (2004 NTB), Symmlin* and (2005 sNME). However, Temodar* (1999 pNME) and Frova (2001 sNME) were developed by pharmaceutical companies, as was Campath* (2001 NTB) although US biotechnology companies took over its clinical development.
- Roughly half of France's and Italy's university drugs were developed by pharmaceutical companies (Arixtra* (2001 pNME), Rebif (2002 sNTB), and Ellence (1999 pNME)), and half, at least initially, by biotechnology companies (Alinia* (2002 pNME), Tyzeka (2006 sNME), and Apokyn* (2004 pNME)).
- All of Belgium's university discoveries, Viread (2001 pNME) and Hepsera (2002 pNME), were developed to marketing by Gilead Sciences.

Note 6. The discovery of Humira (2002) is about 40% attributable to Cambridge Antibody Technology (and indirectly to Cambridge University). Campath (2001) was discovered by Cambridge University. Myozyme (2006) is about 40% attributable to Erasmus University. Rebif (2002) and Erbitux (2004) are probably about 80% and 30%, respectively, attributable to the Weizmann Institute.

The new therapeutic biologics (NTBs) that are more than 20% attributable to pharmaceutical companies are: Xigris (2001), discovered by Lilly; Pegasys (2002), about 50% attributable to Roche's New Jersey laboratory; Humira (2002), about 40% attributable to Knoll's Massachusetts laboratory; Elitec (2002) from a Sanofi-affiliated laboratory); and Mircera (2007) from the Boehringer Mannheim laboratories, which Roche purchased in 1997, and incorporating PEG technology from Nektar.

Including all polypeptide and polynucleotide based drugs within an expanded set of NTBs would bring in the following drugs originating from pharmaceutical companies: Mylotarg (2000 pNME) about 75% attributable to Wyeth/Lederle; Recludan (1998 pNME), which was discovered by Hoescht, probably with input from researchers in Erfurt Medical Academy (see note 1 above); and four recombinant insulins, Lantus (2000), NovoLog (2000), Apidra (2004) and Levemir (2005) (all sNMEs, the first two discovered by Hoescht and the last two by Novo Nordisk).

Note 7. The U→P blockbuster NMEs are Eloxatin (2002), Alimta (2004), Lyrica (2004), Temodar (1999) and Gleevec (2001). All were priority reviewed, but the first three have mechanisms of action and structures similar to those of drugs that had been on the market at least three years prior to their approval. In addition, the last three are only partially attributable to universities.

Note 8. 67 percent of peak year sales of US pNMEs approved 1998–2005 were attributable to blockbusters (drugs with peak year sale over \$1 billion) compared with 45 percent of peak year sales of US sNMEs approved during the same period. For Japan, the equivalent percentages are 97 and 83, respectively; for the UK, 93 and 0; and for Switzerland 72 and 56. Among the top five drug-discovering countries, only Germany is different with 84 percent of sNME peak sales from blockbusters compared with 54 percent of pNME peak sales. This is probably due to NMEs that respond to unmet medical needs (that is, pNMEs) being better positioned to gain large sales than those that do not (that is, sNMEs), although pharmaceutical companies and biotechnology companies must be able to discover such pNMEs or to partner with universities that do. Perhaps, among pharmaceutical companies, this capability is rare outside of US, UK, Swiss and Japanese companies.

The exceptions to blockbuster pNMEs being discovered by pharmaceutical companies are: Tamiflu (1999), Velcade (2003) and Revlimid (2005) discovered primarily in US biotechnology companies; Alimta (2004) and Lyrica (2004) discovered primarily in US universities (together these account for five of the nine blockbuster pNMEs that are primarily of US origin); Eloxatin (2002) from Nagoya City University; and Temodar (1999) about 60 percent attributable to UK academic institutions.

In addition to Eloxatin, Japan's three pNME blockbusters are Xeloda (1998) and Actos (1999). In addition to Temodar, the UK's three pNME blockbusters are Viagra (1998) and Avandia (1999). The high dependence of Japanese and UK pNME sales on just a few blockbusters means these revenues can decline rapidly if sales of one of the blockbusters erode. This probably has happened in the case of Avandia, whose annual sales declined from a peak of about \$2.6 billion in 2006 to about \$950 million in 2008 because of safety concerns.

The only pNME blockbuster attributed to continental Europe (excluding Switzerland) is Zometa (2001) about half (\$690 million) attributable to Boehringer Mannheim and half to Ciba Geigy's Swiss laboratories.

Note 9. 46 of the 54 orphan drugs (85%, including 12 NTBs) were probably priority reviewed, while 42 (78%) are scientifically novel. Among pNMEs, orphan drugs account for 55% of those that are university-discovered, 65% of U→B pNMEs, and 50% of biotech-discovered pNMEs. Among scientifically novel drugs, orphan drugs account for 70% of those discovered by universities, 70% of scientifically novel U→B drugs, and 40% of scientifically novel biotech-discovered drugs.

Note 10. The only example of a non-US biotechnology company developing an orphan drug discovered outside its region is Britannia Pharmaceutical's initial development of Apokyn (2004 pNME for Parkinson's disease), which was discovered by US, UK and Italian academic researchers. UK universities and biotechnology companies also account for the only examples of orphan drug discoveries occurring in non-US universities that were developed by local biotechnology companies. Apart from Apokyn, Zavesca (2003 sNME, 60% attributed to Oxford University), was initially developed by Oxford GlycoSciences.

Note 11. The only other examples of major multinational pharmaceutical companies undertaking development of orphan drugs discovered in universities are Campath (2001 NTB), whose development was abandoned by pharmaceutical companies and taken up by biotechnology companies (Note 2 above) and Refludan (Note 1 above). The following university-discovered orphan drugs were initially developed by mid-size pharmaceutical companies: Curosurf (1999 sNME) transferred from Karolinska to Chiesi Farma, and Somatuline Depot (2007 sNME) transferred from Tulane to Ipsen. Merck KgA obtained FDA approval of Curosurf and went on to market it in the US. A subsidiary of Ipsen obtained FDA approval for Somatuline Depot and then marketed it in the US. All other U→P orphans were taken through FDA approval and then to marketing by biotechnology companies.

Note 12. Six orphan drugs from European pharmaceutical companies were approved first in the US then in Europe: Tracleer (2001 sNME from Roche), Gleevec (2001 pNME from Novartis), Ventavis (2004 pNME from Schering AG), Exjade (2005 pNME from Novartis), Tasigna (2005 sNME from Novartis) and Letairis (2005 pNME from BASF). Rufinamide (Inovelon) from Ciba-Geigy was approved first in Europe for Lennox-Gastaut syndrome, a severe form of epilepsy, and then in 2008 in the US as an sNME.

The three orphan drugs developed by European biotechnology companies or small pharmaceutical companies and approved by the European Commission before approval by the FDA are: Zavesca mainly from Oxford University and initially developed by Oxford GlycoSciences, which was approved by FDA in 2003 as an sNME; carglumic acid (Carbaglu), an old compound whose use to treat N-acetylglutamate synthetase deficiency was demonstrated by French, Austrian and Swiss academic clinical researchers, developed by Orphan Europe and approved by the FDA as a pNME in 2010; and stiripentol (Diacomit) from the small French pharmaceutical company, Biocodex, approved for infant myoclonic epilepsy. Concerns over drug interactions due to its inhibition of cytochrome P450 and other enzymes have delayed Diacomit's approval by the FDA.

Note 13. 54 of the 58 drugs approved in Japan only for orphan indications were discovered outside Japan. Of the 54, 21 have been approved for non-orphan indications in the US, most commonly for HIV/AIDS, which is an orphan indication in Japan, but not in the US. Eight of the 54 were marketed in the US or Europe for at least ten years before they were approved in Japan.

Among the four indigenous Japanese orphan drugs, tamibarotene for acute promyelocytic leukaemia is the closest to FDA approval. It was discovered by University of Tokyo scientists, and initially developed by Toukou Yakuhin, a small Japanese biotech. As of 2010, Phase II trials were underway in Japan and Phase II trials in the US for FDA approval. The US trials were initially sponsored by the US biotech, Innovive, which in 2008 was acquired the biotech, CtyRx.

The likelihood that any of the remaining three Japanese orphan drugs will ever be marketed in North America or Europe is probably low. On the basis of reports by American or European researchers, there may be some interest in developing Otsuka's mozavaptan (Physuline), a vasopressin V2 receptor antagonist for inappropriate antidiuretic hormone syndrome. However, this competes with Astellas's Vaprisol, an sNME approved by the FDA in 2005. There seem to be few reports showing interest in Tanabe's synthetic thyrotropin releasing hormone, taltirelin, approved in Japan for spinocerebellar ataxia; or in the non-recombinant human activated protein C discovered by the Chemo-Sero-Therapeutic

Research Institute in Kumamoto and developed by Teijin. The Japanese health ministry approved the latter in 2000 for thrombocytopenia associated with congenital protein C deficiency. The FDA approved a non-recombinant non-activated human protein C, Ceprotin, for the same indication in 2007 (see note 19, below). Teijin has acquired Japan marketing rights for Lilly's recombinant activated protein C, Xigris (NTB, approved by FDA 2001 for sepsis), and this may reduce its overall interest in taltirelin.

One other Japanese orphan drug initially approved during the same period, a humanized monoclonal IL6 antibody largely discovered in Osaka University, was subsequently approved for rheumatoid arthritis in Japan and the US. Osaka University researchers cloned IL6 in 1986, and began collaborating the same year with Chugai on developing an antagonist. They identified the receptor in 1987, and developed an antibody in 1988. The same year Chugai undertook humanization work and, using technology from UK MRC, succeeded in humanizing the antibody in 1990 (REF. 10). Chugai subsequently developed the antibody as tocilizumab (Actemra) and obtained approval in Japan for Castleman's Disease in 2005 and for rheumatoid arthritis in 2008. In January 2010, the FDA approved Actemra for rheumatoid arthritis.

Note 14. Of the 15 drugs primarily invented or received from universities by Genentech, Amgen, Genzyme and Biogen, 12 were taken all the way to marketing. These are:

- From Genentech (founded in 1976 with about 11,000 employees in 2008): Herceptin (1998 orphan NTB), TNKase (2000 NTB), Raptiva (2003 NTB), Avastin (2004 NTB) and Lucentis (2006 NTB);
- From Amgen (founded 1980, 17,500 employees): Aranesp (2001 NTB), Neulasta (2002 NTB), and Kepivance (2004 NTB with contributions to discovery from NIH/NCI and Chiron);
- From Genzyme (founded 1981, 11,000 employees): Thyrogen (1998 orphan pNME with contributions from Ares), Fabrazyme (2003 orphan NTB from Mount Sinai School of Medicine) and Myozyme (2006 orphan NTB with contributions from Erasmus University, Duke University and Adelaide Children's Hospital, as well as the US biotech, Synpac, which developed an initial, though ultimately not used, cell line production system);
- From Biogen-Idec (4,200 employees in 2009): Amevive (2003 NTB), which Biogen co-discovered with Harvard and University of Michigan. Biogen was founded in 1978, and merged with Idec in 2003 to form Biogen-Idec.

Note 15. The fifteen non-orphan drugs developed by the same biotechnology company other than one of the big four (previous note) all the way from discovery (or university transfer of discovery) through the initial year of marketing in the US are: (* indicates scientifically novel)

- Renagel (1998 sNME from Harvard and GelTex);
- Enbrel (1998 NTB* from MGH and Immunex);
- Synagis (1998 NTB* from Medimmune);
- Hecetrol (1999 sNME from University of Wisconsin and Bone Care);
- Levulan Kerastick (1999 sNME* from Queens University, Ontario, and DUSA);
- Visudyne (2000 pNME* from UBC and QLT PhotoTherapeutics);
- Natrecor (2001 sNME* from California Biotech which later changed its name to Scios);
- Viread (2001 pNME from the Czech Academy of Medical Science, Catholic University of Leuven and Gilead);
- Hepsera (2002 pNME from the Czech Academy of Medical Science, Catholic University of Leuven and Gilead);
- Plenaxis (2003 pNME* from Indiana University and Praecis);
- Byetta (2005 sNME* from Mount Sinai Sch of Medicine, Bronx VA Hospital and Amylin);
- Symlin (2005 sNME* from Oxford and Amylin);

- Amitiza (2006 sNME* from RTech Ueno and its US subsidiary, Sucampo);
- Azilect (2006 sNME from Technion and Teva); and
- Tyzeka (2006 sNME from Montpellier University, other European universities and Noviro/Idenix).

These account for the largest proportion of the 39 B/U→B drugs taken all the way from discovery to market by a single biotechnology company, the remainder being evenly divided between those from the largest biotechnology companies, and other drugs that are orphans. The respective mean peak year sales for these three groups are a respectable \$790 million, \$2,100 million (this group includes blockbusters such as Herceptin (1998), Avastin (2004), Aranesp (2001), Neulasta (2002) and Lucentis (2006)), and \$220 million.

Note 16. Notes 1 and 2 above outline the histories of Gleevec and Campath. See also the history of Eloxatin in Note 2, which was initially developed by a metals company and then taken up by a biotechnology company. Furthermore, it might be argued that May & Baker, co-discoverer of Temodar along with UK academics, should not be considered a major multinational pharmaceutical company. Schering-Plough later obtained rights to the drug and obtained FDA approval. Aside from Arixtra, the only other scientifically novel drugs from universities that were initially developed by multinational pharmaceutical companies in the period analysed are probably:

- Ferrlecit (1999 pNME, peak sales probably about \$150 million in 2005) discovered many years ago at Humbolt University, Berlin, and marketed initially in Europe by Rhone Poulenc;
- Reminyl (2001 sNME, peak sales about \$580 million in 2008) whose utility for Alzheimer's was probably demonstrated mainly by researchers in Free University Berlin and Mount Sinai Medical Center and which was commercialized in part by Shire (biotech) and Janssen (by that time a subsidiary of Johnson and Johnson);
- Cetrotide (2000 sNME) from Tulane developed to the point of FDA approval by Asta Medica, the pharmaceutical subsidiary of the German fine chemical company, Degussa.

Note 17. Despite the overall and proportional decline over the ten years of this study in drugs discovered in pharmaceutical companies and biotechnology companies, the latter half of the study period saw an increase in pNMEs from US pharmaceutical companies. Some of these drugs are not scientifically novel. So far only one, Tarceva (2004) has achieved blockbuster sales, and many still have low sales. Most are for cancer or infectious disease. Also three scientifically novel drugs primarily from UK pharmaceutical companies were approved in 2007, although none were approved in the preceding three years.

The following are the pNMEs attributable mainly to US pharmaceutical companies that were approved in the last half of the study catchment period. (* indicates scientifically novel drug. [O] indicates orphan. † indicates laboratory closed or reorganized and no longer focusing on human pharmaceutical R&D):

- 2003: Cubicin* (\$455 M py sales to 2008. Lilly, Indianapolis)
- 2004: Tarceva* (\$1581M. Pfizer, Groton);
- 2005: Aptivus* (\$83M. Upjohn, Kalamazoo[†]), Arranon*[O] (\$60M. Burroughs, Research Triangle), Baraclude (\$541. Bristol-Myers, Princeton), Nevanac (\$60M. A.H. Robins, Richmond; Alcon, Ft. Worth), Nexavar*[O] (\$679M. Bayer, West Haven, CT[†]), and Tygacil (\$216M. American Cyanamid, Pearl River, NY);
- 2006: Chantix* (\$841M. Pfizer, Groton), Noxafil (\$149M. Schering-Plough, Kenilworth, NJ), Sprycel* (\$310M. Bristol-Myers, Princeton) and Prezista \$304M. Searle, St. Louis with contribution from Tibotec, NIH and U of Illinois at Chicago) and
- 2007: Ixempra* (\$101M. Bristol-Myers, Princeton) and Toricel [O] (\$122M. Wyeth, Princeton and Pearl River).

The three scientifically novel drugs from UK pharmaceutical companies approved in 2007 are Altabax (sNME), Selzentry (pNME) and Tykerb (pNME).

Year by year fluctuations are considerable, so these recent approvals do not necessarily signal a trend towards more innovative drug discovery in pharmaceutical companies. Also, two of the US pharmaceutical company-derived pNMEs are from laboratories now closed or re-organized away from human pharmaceutical R&D, and three others are from Wyeth or Schering-Plough which have recently merged.

Note 19. This statement is based upon an analysis of the 16 drugs among the 252 whose key patents had co-inventors from both universities and large established companies, or where there was otherwise clear evidence of pharmaceutical company-university collaboration at critical phases of discovery. Among these, the two drugs that arose in substantial part from collaborations with US universities, (Gleevec (2001) and Lyrica (2004), were both pNMEs and Gleevec was scientifically novel. Among the three that arose in substantial part from collaborations with UK universities; Temodar (1999 pNME), Campath (2001 NTB) and Frova (2001 sNME); the former two were scientifically novel. However, among the other 11, twice as many are sNMEs as pNMEs.

Note 19. This note presents the origins of nine NTBs approved by FDA’s Center for Biologics Evaluation and Research (CBER) between 1998-2007 that embody advanced technologies similar to those used in the development or manufacture of CDER-approved NTBs.

The following tables list these drugs and summarize their origins based on REF. 11, available patents and articles written by the inventors.

Summary table

US trade name	Biological name and function	Approval year	Attribution of discovery
NovoSeven*	Recombinant coagulation Factor VIIa for bleeding episodes in hemophilia patients	1999 (EU 1996)	Zymogenetics (US biotech) with production discoveries from Novo Nordisk (DK)
CroFab*	Snake venom anti-sera	2000	UK researcher probably based in an academic hospital, 1st transfer to UK biotech
Refacto	Recombinant coagulation Factor VIII for haemophilia	2000	Primarily Pharmacia (Sweden), drawing on earlier discoveries by Genentech, Genetics Institute (which both had developed and manufactured earlier versions of recombinant factor VIII) and maybe Behring GmbH (which has patents covering the manufacture of recombinant factor VIII without using albumin).
DigiFab	Antibody based therapy for digoxin toxicity	2001	Probably Protherics (US biotech)
Aralast	Alpha1-Proteinase Inhibitor for emphysema due to congenital alpha1-proteinase inhibitor deficiency	2002	Probably Alpha Therapeutic Corp. (US biotech)
Advate	Recombinant coagulation Factor VIII for haemophilia	2003	Primarily Baxter (US), probably drawing on the same earlier discoveries as Refacto (above)
Zemaira	Alpha1-Proteinase Inhibitor for emphysema due to congenital alpha1-	2003	Behring GmbH (probably Behring’s German lab)

	proteinase inhibitor deficiency		
Ceprotin	Human plasma-derived Protein C, precursor of the anti-coagulant activated Protein C, approved to treat congenital protein C deficiency and (in Europe) purpura fulminans	2007	Probably Immuno Aktiengesellschaft (Austria)
Evithrom	Human thrombin	2007	Probably Omrix (Israeli biotech)

* Probably scientifically novel.

The distribution among type of inventing organization is:

Organization	Number of attributable drugs	Of which novel
Pharma	3.8	0.2
Biotech	4.2	0.8
University transferring 1 st to biotech	1	1
Total	9	2

The distribution among countries of origin is:

Country	Number of attributable drugs	Of which novel
US	4	0.8
UK	1	1
Germany	1	
Denmark	0.2	0.2
Sweden	0.8	
Austria	1	
Israel	1	
Total	9	2

In summary, the origins of these drugs are only modestly less dominated by biotechnology companies compared with the CDER approved NTBs. The most notable difference compared with the CDER approved NTBs is the significant contribution of Continental European laboratories.

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