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e-companion

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Electronic Companion—"Valuing R&D Projects in a Portfolio: Evidence from the Pharmaceutical Industry" by Karan Girotra, Christian Terwiesch, and Karl T. Ulrich, *Management Science*, DOI 10.1287/mnsc.1070.0703.

Online Supplement

EC.1. FAQS for Hypothesis 2

Q. What do the discount factors mean?

A. These discount factors capture the impact of a delay in product introduction to the market. This could be due to the time value of money or changed market conditions- lower margins, increased competition, loss of market share, etc. Hendricks and Singhal (1997) rigorously study the impact of such delays.

Q. Is the proportionality constant the same for different drugs?

A. Different drugs may have different market sizes and thus the proportionality constant may not be the same across all failures in our sample. Accurate estimates on the market size of a drug are hard to come by, since they are strongly influenced by the drug label, which is only issued by the FDA *after* the successful completion of all clinical trials. Also, the competitive position of the drug is not easy to predict before the results of all trials are known. Therefore, we do not include the market size in our TAPIS metric, and our developed hypothesis will test the role of interaction between compounds targeting the same market, ceteris paribus. In other words, we test if *on an average*, the change in probability is related to the financial impact of the failure. This process reduces the explanatory power of our estimation and makes it less likely that we will find support for our hypothesis. If we had accurate market size data, we could include that in the TAPIS metric and proceed with the same empirical design and possibly have better results.

Q. Does this hypothesis tell me how many backup drugs should I develop?

Q. Are backup drugs always useful even if they cost a lot?

Q. Why don't you include the additional development costs because of backup drugs in your hypothesis?

A. Note that in formulating the financial impact of a failure, we did not include the development costs already incurred by the firm for development of multiple compounds. A firm that has more backup compounds has already invested in the development of these multiple compounds till the current stage of development and *has already incurred* higher development costs; these *sunk* development costs are not influenced by the failure and thus do not appear in our hypothesis. Our hypothesis captures the value of a compound or the impact of a failure, *given* the choices made by the firm with respect to the number of parallel development efforts. It *does not* advise on the optimal number of development efforts. Ding and Eliashberg (2002) provide guidance on the number of parallel development efforts to pursue.

There is an effect of failure on development costs *subsequent* to the failure, related to the failure-induced higher probability of phase I, phase II compounds now being brought into phase III trials, and thus higher development costs. We believe this is a minor second order effect and we don't capture this effect in our hypothesis.

Q. What if the success/failure of different drugs in a firm's portfolio is not independent?

A. In developing the hypotheses, we keep in mind that for empirically testing the developed theory, we will need to compute these probabilities using available data. With the data available to us, we

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can not estimate the correlation structure between different drugs and thus, we assume that the trials are independent. If detailed data would be available such that the correlation structure between the different compounds can be estimated (for instance on the basis of the mechanism of action of the drug); the expressions in our analysis can be suitably modified to capture the correlations. The rest of the empirical analysis would proceed in the same way.

Even with the availability of data, developing a scientific approach to estimating the correlation structure between different compounds is a challenging problem that is not well understood by product development researchers or the pharmaceutical industry. Addressing this is the focus of our ongoing research.

EC.2. The Event Study Methodology

EC.2.1. Return Generating Models

The three return-generating models for expected returns that we use are–

The Comparison Period Mean Model (*CP*). The comparison period mean model uses the average return on the firm's stock over the estimation period as the expected return on the stock. The abnormal return is computed as the difference between the return on the days of the event and the average return on the firm's stock over the estimation period.

The Market Model (*MM*) (MacKinlay 1997)*:* The Market model posits a linear relationship between the return on a firm's stock and the return on the market portfolio. According to the market model, for any firm i, the expected return at time t, R_i^t, is given by Equation (EC1); where R_M^t is the period-t return on the market index, Ω^{t-1} is the information set available to the market about the firm at time $t-1$.

$$\mathrm{E}[R_i^t \mid \Omega^{t-1}] = \alpha_i + \beta_i R_M^t \tag{EC1}$$

We use the CRSP equally weighted index[EC1] as a proxy for the market portfolio. α_i and β_i are firm-specific parameters that are estimated using estimation-period historical data for *each* event in the sample.

The Fama-French Three Factor Model (*FF*) (Fama and French 1996): The model posits the return generating process described in Equation (EC2). β_i is the sensitivity of the stock returns to market returns; s_i is the sensitivity of the stock returns to the difference between small and large capitalization stock returns and h_i is the sensitivity of the stock returns to the difference between the returns on value and growth stocks.[EC2]

$$\mathrm{E}[R_i^t \mid \Omega^{t-1}] = \alpha_i + \beta_i R_M^t + s_i SMB^t + h_i HML^t \tag{EC2}$$

We use the broad based CRSP equally weighted index as a proxy for the market portfolio. α_i, β_i, s_i, and h_i are firm-specific parameters that are estimated using historical data for each event in the sample.

The component of the return that *can not* be explained by the above described market models, is attributed to the event, in our case the failure of the phase III clinical trials. This component is commonly referred to as the abnormal return, AR_i^t described in Equation (EC3).

$$AR_i^t = R_i^t - \mathrm{E}[R_i^t \mid \Omega^{t-1}] \tag{EC3}$$

If no new information is available between the period $t-1$ and t, we would expect that $\mathrm{E}[AR^t] = 0$.

[EC1] The CRSP equally weighted index is an index provided by the Center for Research in Security Prices (CRSP), a financial research center at the Graduate School of Business at The University of Chicago. The index gives all securities an equal weight.

[EC2] SMB^t is defined as the average return on three small market capitalization portfolios minus the average return on three large market capitalization portfolios; HML^t is defined as the average return on two high book-to-market equity portfolios minus the average return on two low book-to-market equity portfolios. (See Fama and French 1993 for detailed explanations of SMB^t and HML^t.) The factors- SMB^t and HML^t are obtained from Prof. Kenneth R. French's website (http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/index.html).

EC.2.2. Finding the Event Window Using Trading Volumes

Often the impact of an event is not limited only to the day of the announcement. Information about the event may leak before the announcement (a speculative article in the press, rumors at the financial market, etc.) or markets may take a few sessions to fully price the impact of the event. Moreover, the exact time of the day when the drug failure announcement is made may not be known. The announcement may have been made after trading hours on the day of the announcement and in such a scenario, the stock price is not affected until the next trading session. Most event studies include the abnormal return for a few days before and after the event is used when constructing a measure to incorporate the full impact of the event. This measure is often referred to as the cumulative abnormal return or CAR_i (Equation (EC4)), where the period (t_1, t_2) is called the event window.

$$CAR_i = \sum_{t=T+t_1}^{t=T+t_2} AR_i^t \tag{EC4}$$

To identify the appropriate event window, Tkac (1999) suggests using the number of shares traded or the trading volume. As the market incorporates the new information, market participants adjust their positions leading to higher trading volume than under normal circumstances. Tkac (1999) also provides a theoretical model for the normal or the expected trading volume (Equation (EC5)).

$$\mathrm{E}[V_i^t] = \gamma_i + \delta_i MV^t \tag{EC5}$$

In Equation (EC5) the expected trading volume for firm i at time t, $\mathrm{E}[V_i^t]$, is explained using the trading volume in the market MV^t. The factors γ_i and δ_i are estimated using historical data for *each* event in the sample. The abnormal volume, AV_i^t, is then given as the excess of the actual volume over the expected volume (EC6).

$$AV_i^t = V_i^t - \mathrm{E}[V_i^t] \tag{EC6}$$

We compute the abnormal trading volume averaged across the events and define the event window to include days before and after the event that have a statistically significant positive average abnormal trading volume.[EC3] The event window identified allows us to compute the Cumulative Abnormal Return and the loss in market capitalization[EC4] associated with each drug failure in our sample.

EC.3. Probability Estimation

To estimate the probabilities (p_1, p_2, p_3), we use data on all clinical trials in the ADIS database. A vast majority of these trials are run by firms that are not publicly traded and don't otherwise appear in our sample. Danzon et al. (2005) finds that the indication explains the largest fraction of the variance in the odds of success and failure between different drugs. Thus, we estimate p_i at the level of an indication and assume that all drugs for an indication at the same stage of development have the same odds of failure. For example, to determine p_i for an Alzheimer's drug, we look at the performance of all Alzheimer's drugs irrespective of originating firm. p_i is the probability of failure of a drug currently undergoing phase i trials, *during phase i trials or in any subsequent stage*(*s*) for the disease in question. If the probability of success in phase i is given as $s_i \in [0, 1]$; $p_i = 1 - \prod_{k=i}^{3} s_i$. To compute p_1, p_2, and p_3, we use estimates on s_1, s_2, and s_3. Each s_i is estimated by looking at the average success rate in the indication of concern.

$$s_i = \frac{\#\ of\ Successful\ Phase\ i\ Trials}{Total\ \#\ of\ Completed\ Phase\ i\ Trials} \tag{EC7}$$

In Table EC.1, we provide the values of (p_1, p_2, p_3), computed from the estimated (s_1, s_2, s_3). The numbers in parens denote the number of compounds or data-points used to estimate (s_1, s_2, s_3). For a small fraction of indication-phase pairs (36 out of 282), the number of total completed trials is less than 4. For these indication-phase pairs the estimates on s_i may not be reliable, in such cases, we substitute the indication-specific success rate with an average success rate across all indications. Such indication-phase pairs are denoted by a "*" in Table EC.1. The number in parens for such cases is the total pooled number of phase i compounds used for that estimation.

[EC3] This is analogous to the market model for stock returns, and is often referred to as a volume event study.

[EC4] Change in Market Capitalization = Shares Outstanding * Price * Cumulative Abnormal Return.

Table EC.1

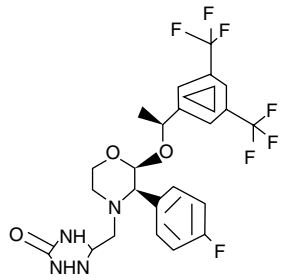
Sno.	Indication/disease	p_1	p_2	p_3
1	*Acute myeloid leukaemia*	0.826 (20)	0.677 (13)	0.4 (5)
2	*Alzheimer's disease*	0.926 (79)	0.76 (47)	0.636 (22)
3	*Amyotrophic lateral sclerosis*	0.973 (11)	0.833 (6)	0.8 (5)
4	*Anxiety disorders*	0.992 (55)	0.935 (28)	0.833 (12)
5	*Arrhythmias*	0.987 (28)	0.943 (30)	0.714 (7)
6	*Arterial thrombosis*	0.785 (4)	0.732 (6)	0.197* (3,147)
7	*Asthma*	0.809 (152)	0.709 (109)	0.226 (53)
8	*Atherosclerosis*	0.831 (28)	0.732 (9)	0.197* (3,147)
9	*Atopic dermatitis*	0.718 (25)	0.657 (10)	0.143 (14)
10	*Attention-deficit hyperactivity disorder*	0.617 (14)	0.464 (12)	0.286 (7)
11	*Bacterial infections*	0.616 (60)	0.385 (42)	0.109 (46)
12	*Basal cell cancer*	0.967 (6)	0.8 (6)	0.8 (5)
13	*Benign prostatic hyperplasia*	0.58 (27)	0.542 (16)	0.083 (12)
14	*Bladder cancer*	0.563 (18)	0.444 (12)	0.167 (6)
15	*Breast cancer*	0.599 (120)	0.52 (59)	0.114 (35)
16	*Cancer*	0.862 (181)	0.777 (74)	0.176 (34)
17	*Cardiovascular disorders*	0.738 (9)	0.55 (5)	0.25 (4)
18	*Catabolism*	0.552* (5,900)	0.4* (3,740)	0.197* (3,147)
19	*Cerebrovascular disorders*	0.678 (6)	0.599 (6)	0.197* (3,147)
20	*Chemoprotection*	0.79 (19)	0.625 (10)	0.375 (8)
21	*Chronic obstructive pulmonary disease*	0.752 (41)	0.589 (23)	0.273 (11)
22	*Colorectal cancer*	0.705 (104)	0.621 (41)	0.182 (11)
23	*Congestive heart failure*	0.73 (34)	0.535 (26)	0.364 (11)
24	*Coronary artery restenosis*	0.858 (16)	0.74 (12)	0.375 (8)
25	*Depression*	0.911 (78)	0.747 (60)	0.525 (40)
26	*Diabetes mellitus*	0.826 (26)	0.657 (14)	0.4 (5)
27	*Diabetic complications*	0.785 (10)	0.732 (9)	0.197* (3,147)
28	*Diabetic neuropathies*	0.948 (27)	0.825 (19)	0.667 (6)
29	*Diabetic retinopathy*	0.356 (4)	0.197 (5)	0.197* (3,147)
30	*Diagnostic imaging*	0.516 (32)	0.269 (23)	0.269 (26)
31	*Diarrhoea*	0.742 (9)	0.502* (3,740)	0.333 (6)
32	*Emesis*	0.59 (16)	0.427 (20)	0.182 (11)
33	*Epilepsy*	0.836 (30)	0.619 (17)	0.353 (17)
34	*Erectile dysfunction*	0.52 (22)	0.4 (16)	0.2 (15)
35	*Fracture treatment*	0.518 (4)	0.4* (3,740)	0.197* (3,147)
36	*Gastric ulcer*	0.738* (5,900)	0.625 (4)	0.25 (12)
37	*Glioblastoma*	0.678 (15)	0.599 (6)	0.197* (3,147)
38	*Glioma*	0.926 (27)	0.8 (16)	0.6 (5)
39	*Graft-versus-host disease*	0.896 (14)	0.714 (14)	0.636 (11)
40	*Gram-positive infections*	0.555* (5,900)	0.402* (3,740)	0.2 (5)
41	*HIV-1 infections*	0.833 (28)	0.688 (16)	0.375 (8)
42	*Head and neck cancer*	0.842 (47)	0.697 (22)	0.444 (9)
43	*Head injuries*	0.993 (9)	0.9 (10)	0.875 (8)
44	*Heart failure*	0.814 (33)	0.665 (39)	0.346 (26)
45	*Hepatitis B*	0.291 (27)	0.237 (24)	0.036 (28)
46	*Herpes simplex virus infections*	0.841 (12)	0.688 (16)	0.444 (9)
47	*Herpes zoster*	0.586* (5,900)	0.333 (5)	0.333 (6)
48	*Huntington's disease*	0.4* (5,900)	0.197 (4)	0.197* (3,147)
49	*Hypercholesterolaemia*	0.552 (22)	0.497 (13)	0.067 (15)
50	*Hyperlipidaemia*	0.91 (37)	0.739 (17)	0.444 (9)
51	*Hypertension*	0.783 (88)	0.638 (76)	0.19 (63)
52	*Irritable bowel syndrome*	0.904 (28)	0.748 (17)	0.571 (7)
53	*Ischaemic heart disorders*	0.988 (28)	0.924 (23)	0.75 (12)
54	*Leukaemia*	0.62 (19)	0.492 (7)	0.111 (9)
55	*Malaria*	0.455 (11)	0.333 (6)	0 (5)
56	*Malignant hypertension*	0.552* (5,900)	0.4* (3,740)	0.197* (3,147)
57	*Migraine*	0.737 (42)	0.558 (21)	0.286 (14)
58	*Multiple myeloma*	0.651 (31)	0.484 (16)	0.25 (8)
59	*Multiple sclerosis*	0.877 (37)	0.706 (17)	0.5 (10)
60	*Muscle wasting*	0.552* (5,900)	0.4* (3,740)	0.197* (3,147)
61	*Musculoskeletal pain*	0.354* (5,900)	0.167 (4)	0.167 (6)

Table EC.1 (Continued)

Sno.	Indication/disease	p_1	p_2	p_3
62	*Myocardial infarction*	0.766 (37)	0.622 (32)	0.364 (22)
63	*Neuropathic pain*	0.731 (23)	0.625 (10)	0.25 (4)
64	*Neutropenia*	0.707 (5)	0.531 (8)	0.375 (8)
65	*Non-small cell lung cancer*	0.877 (108)	0.715 (46)	0.563 (16)
66	*Osteoarthritis*	0.506 (21)	0.404 (26)	0.032 (31)
67	*Ovarian cancer*	0.816 (77)	0.707 (42)	0.353 (17)
68	*Pain*	0.647 (74)	0.523 (46)	0.156 (32)
69	*Pancreatic cancer*	0.905 (58)	0.772 (31)	0.583 (12)
70	*Parkinson's disease*	0.721 (47)	0.543 (23)	0.3 (20)
71	*Peptic ulcer*	0.929 (21)	0.794 (27)	0.444 (18)
72	*Peripheral nerve disorders*	0.678 (4)	0.599 (4)	0.197* (3,147)
73	*Picornavirus infections*	0.552* (5,900)	0.4* (3,740)	0.197* (3,147)
74	*Postmenopausal osteoporosis*	0.51 (47)	0.313 (39)	0.162 (37)
75	*Postoperative pain*	0.557 (18)	0.416 (14)	0.091 (11)
76	*Psychotic disorders*	0.868 (19)	0.667 (12)	0.5 (8)
77	*Renal cancer*	0.925 (72)	0.814 (23)	0.571 (7)
78	*Rheumatic disorders*	0.76 (12)	0.621 (16)	0.241 (29)
79	*Rotavirus infections*	0.5* (5,900)	0.331 (6)	0.197* (3,147)
80	*Schizophrenia*	0.711 (36)	0.628 (25)	0.154 (13)
81	*Septic shock*	0.992 (19)	0.913 (13)	0.875 (8)
82	*Small cell lung cancer*	0.753 (25)	0.63 (9)	0.333 (9)
83	*Somatotropin deficiency*	0.325 (6)	0.1 (6)	0.1 (10)
84	*Spinal cord injuries*	0.678 (6)	0.599 (4)	0.197* (3,147)
85	*Stem cell mobilisation*	0.518 (4)	0.4* (3,740)	0.197* (3,147)
86	*Stroke*	0.939 (54)	0.772 (38)	0.667 (18)
87	*Systemic lupus erythematosus*	0.839 (6)	0.799 (4)	0.197* (3,147)
88	*Thrombocytopenia*	0.964 (12)	0.825 (10)	0.75 (4)
89	*Thrombosis*	0.862 (65)	0.697 (34)	0.357 (14)
90	*Transplant rejection*	0.784 (20)	0.619 (7)	0.333 (9)
91	*Tuberculosis*	0.669 (7)	0.518 (5)	0.197* (3147)
92	*Type-2 diabetes mellitus*	0.612 (76)	0.515 (48)	0.105 (19)
93	*Ulcerative colitis*	0.905 (30)	0.762 (18)	0.571 (7)
94	*Unstable angina pectoris*	0.818 (15)	0.658 (18)	0.385 (13)

EC.4. Sample Data Entry from the ADIS Data Set

Aprepitant (EMEND, L 754030, MK 0869, MK 869)



Chemical Name: 5-(2(*R*)-(1(*R*)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3(*S*)-(4-fluorophenyl) morpholin-4-ylmethyl)-3,4-dihydro-2H-1,2,4-triazol-3-one
Molecular Formula: C23 H21 N4 F7 O3

CAS Number: 170729-80-3; 170902-81-5 ((1S)-isomer); 172822-28-5 ([2S(1S),3S]-isomer); 172822-29-6 ([2S(1R),3R]-isomer)

WHO ATC Code: A04A-D (Other antiemetics);
N06A-X (Other antidepressants)

EphMRA ATC Code: A4A9 (Other Antiemetics and Antinauseants);
N6A (Anti-Depressants and Mood Stabilisers)

Originator Companies: Merck & Co
Last Update: 2003-12-15
Accession Number: 9602

Drug Development History
15-12-2003—Clinical data from a media release have been added to the pharmacokinetics section (9029028)
11-12-2003—Sales forecasts reviewed by Lehman Brothers
14-11-2003—Discontinued—Phase-III for Depression in USA (PO) → Failure in Phase III Clinical
07-08-2003—Studies have been added to the adverse events and Advances in the Treatment of Nausea and Migraine therapeutic trials sections (897818,897819)
23-07-2003—Sales forecasts reviewed by Lehman Brothers
05-06-2003—Data presented at the 39th Annual Meeting of the American Society of Clinical Oncology (ASCO-2003) have been added to the Nausea and migraine therapeutic trials section (9021600)
22-05-2003—Launched for Emesis in USA (PO)
08-05-2003—Data has been added to the drug interactions section (941574)
16-04-2003—Data from a media release have been added to the adverse events and Nausea and migraine therapeutic trials sections (9019583)
10-04-2003—Sales forecasts reviewed by Lehman Brothers
01-04-2003—Registered for Emesis in USA (PO)
31-03-2003—Merck & Co. Inc. has received an approvable letter from the FDA for aprepitant in acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy (www.merck.com)
13-12-2002—Preregistration for Emesis in USA (PO)
12-12-2002—Sales forecasts reviewed by Lehman Brothers
12-09-2002—Sales forecasts reviewed by Lehman Brothers
31-05-2002—Phase-III clinical trials in Depression in USA (PO)
30-05-2002—Sales forecasts reviewed by Lehman Brothers
19-03-2002—Phase-III clinical trials in Emesis in USA (PO)
04-12-2001—Sales forecasts reviewed by Lehman Brothers
24-07-2001—Discontinued-II for Schizophrenia in USA (PO)
14-05-2001—Predicted peak sales have been added
25-08-2000—A study has been added to the Advances in the Treatment of Nausea and Migraine therapeutic trials section (835407)
09-06-1999—Data have been added to the adverse events and the Affective disorders therapeutic trials sections (747155)
17-05-1999—Phase-II clinical trials for Schizophrenia in USA (PO)
17-05-1999—Phase-II clinical trials for Anxiety disorders in USA (PO)
17-02-1999—A study has been added to the Advances in the treatment of nausea and migraine therapeutic trials section (736323)
29-01-1999—Phase-II clinical trials for Emesis in USA (PO)
29-01-1999—Suspended-II for Depression in USA (PO)
22-09-1998—A study has been added to the adverse events and the Affective disorders therapeutic trials events sections (632240)
09-01-1998—Phase-II clinical trials for Depression in USA (PO)
09-01-1998—New profile

EC.5. Associated News Report from Factiva

Merck Ends Research on Once-Promising Antidepressant

By Peter Landers
1123 words
13 November 2003
The Wall Street Journal
B1
English

MERCK & CO. abandoned a depression drug it had been working on for more than a decade.

The company said the drug, known generically as aprepitant, failed to show advantages over a placebo in a large human trial. The decision leaves Merck, once renowned for its research prowess, with one of the thinnest pipelines among major drug makers. Without new products, Merck's future is in danger because its anticholesterol blockbuster Zocor will lose U.S. patent protection in 2006.

The failure of aprepitant is also a major setback for depression patients who don't respond to the class of drugs called selective serotonin reuptake inhibitors, such as Eli Lilly & Co.'s Prozac, Pfizer Inc.'s Zoloft and GlaxoSmithKline PLC's Paxil, or who can't handle their side effects. Doctors say some 40% of people who take SSRIs experience sexual problems, fueling the search for an alternative. "It's really too bad. I definitely was hoping for some new options," says Carol Peyser, a psychiatrist in Redwood City, Calif., who frequently prescribes antidepressants.

The failed drug trial may raise new questions about Merck Chief Executive Raymond Gilmartin, who angered investors last month when he announced that the company wouldn't meet its profit forecast for this year. Mr. Gilmartin is under growing pressure to prove he can turn around Merck, which expects net income to fall this year to $2.90 to $2.95 per share, down from $3.14 per share in 2002.

Antidepressants are a $17 billion market, and Merck was hoping to grab a big chunk of that. Aprepitant has its origins in research that Merck undertook in the early 1990s on a mysterious brain chemical called substance P. (The "P" stands for "powder," the form in which substance P was first isolated in 1931.) In the 1980s, scientists believed that substance P was involved in transmitting pain messages among the brain's neurons, and drugs blocking substance P were tried out as painkillers.

Those studies bore little fruit, but scientists at Merck came to believe that substance P actually worked as a mood depressant—one that had a useful function in normal people but might cause disease if it got out of control. Merck chemists, meanwhile, cooked up aprepitant, a pill that blocks substance P from landing at receptors in the brain's neurons.

The project's shining moment came in 1998, when Merck published a study in the journal Science showing that aprepitant was significantly superior to a placebo in treating depression in a trial of 213 patients. Equally important, the study showed fewer cases of sexual dysfunction in those taking aprepitant compared with Paxil.

But as Merck continued testing aprepitant, the project took a negative turn. The results of a trial that had been intended to ascertain the proper dose of aprepitant shocked the company: None of the proposed doses was superior to a placebo. The study was never published, although the company discussed it at scientific meetings in 2001.

Many companies would have stopped their research at that point. But Mr. Gilmartin said in an interview this past June that Edward Scolnick, Merck's research chief at the time of the dosage study, urged him to keep funding the depression program. One idea was to try out a separate substance P blocker called "compound A" in severely depressed patients. That trial showed good results and convinced Merck that substance P was indeed a factor in depression.

Separately, Merck scientists developed an elaborate brain-scanning system using radioactive tracers to test whether aprepitant was sufficiently hitting the substance P receptors in the brain. The scientists feared the failed trial might have been caused by the drug's difficulty in reaching the brain, but the scans showed that the drug was indeed hitting its target.

Perhaps the most important reason for Merck to keep betting on its depression program was its shortage of other good drugs in development. Currently, its pipeline has only three other drugs in large-scale testing: a tweak to its existing painkiller, Vioxx; a vaccine against cervical cancer; and a diabetes drug bought from a Japanese company. As recently as Oct. 22, Mr. Gilmartin named aprepitant as one of the drugs in Merck's pipeline that suggested the company has a bright future.

Monday-morning quarterbacks may question Merck's decision to fund the big trial in the face of the earlier failed trial and the lack of solid scientific evidence that substance P plays a role in depression. Mr. Gilmartin, a former executive for a medical-devices company, had no experience in pharmaceuticals prior to taking the Merck job in 1994 and often deferred to Dr. Scolnick, a Harvard Medical School graduate who had supervised blockbusters such as Vioxx.

"In a pharmaceutical company it is often difficult to stop advanced projects, especially if you have a strong R&D director," says Max Noble, managing director of Britannia Pharmaceuticals Ltd., a small company based near London.

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Peter Kim, who replaced Dr. Scolnick as head of research at the beginning of this year, defended the decision to pursue aprepitant. "There are significant challenges in scientific research, and unfortunately, sometimes disappointments," Dr. Kim said in a statement. He said Merck would continue studying other psychiatric drugs.

The failure of aprepitant illustrates how difficult depression trials can be. Doctors have trouble distinguishing patients who are clinically depressed from those who are simply going through a rough patch. In addition, even depressed patients may get better temporarily for no particular reason. As a result, the placebo arm of depression trials can show a response rate of 50% or more.

Pfizer is still working on substance P blockers in depression. Some companies are pursuing ways to block corticotrophin releasing factor, or CRF, which may be overactive in depressed patients. AstraZeneca PLC is trying an approach to improving serotonin flow. "I am hopeful that over the next decade we will have therapies," says Gil Block, who heads the company's depression research.

One small consolation prize for Merck: In its exhaustive examination of aprepitant's properties, it discovered that the drug has an antinausea effect. This year, the company received approval to sell aprepitant under the brand name Emend as a treatment for nausea induced by chemotherapy. U.S. sales of Emend were $4 million in the third quarter, or 0.1% of Merck's total U.S. sales.

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