Appendix G

Estimating the Cost of Producing and Selling New Chemical Entities

To estimate the net returns on new chemical entities (NCEs) introduced in the period 1981-83, the cost of manufacturing, marketing and distribution in each year following market approval must be subtracted from net revenues. Precise estimation of such costs is impossible from published financial statements because companies produce a variety of products but report costs on a consolidated basis across all operations. [1] The Office of Technology Assessment (OTA) made assumptions about the costs of manufacture, distribution and marketing based on a variety of sources of data, including a review of the annual reports of six research-intensive U.S.-owned pharmaceutical firms,[2] as detailed below.

Manufacturing and Distribution Costs

The reported annual cost of goods sold for the six companies was used as an approximate estimate of the manufacturing and distribution costs of pharmaceuticals. The sales-weighted average ratio of cost of goods sold to total company sales for the sample of firms was 0.255. These costs include charges for depreciation on facilities and equipment used to produce, store, and distribute the firm's products. OTA estimated the cash outlays for construction of facilities and equipment separately; consequently the estimated depreciation charges associated with the cash outlays were deducted from the cost of goods sold. (The estimated construction costs of $25 million per NCE, for example, were assumed to generate depreciation charges over an average 20-year time horizon. Thus, $1.25 million per year was deducted from the cost of goods sold in each of the 20 years of the product's life.)

Plant and Equipment Costs

Firms make investments in plant and equipment early in the product life cycle, typically before the drug receives approval for marketing. Additional investments may be necessary as time goes on, especially if the drug is one that has a high unit volume. OTA had little specific information to go on to estimate average expenditures for plant and equipment across all drugs. Such investments may vary systematically among types of drugs, especially between biological and synthetic chemicals,

One difference between traditional synthetic compounds and biotechnology and other biological drugs is the ease with which ''campaign' product manufacturing can be undertaken. Product campaigning refers to the scheduling of production runs of different products on the same equipment and using the same facility. Campaign production generally reduces fixed facility costs because it allows different products to share the same facility and equipment and reduces down time of equipment. Costs are incurred in preparing the facility and equipment for new production runs, but the overall manufacturing process is generally cheaper when dedicated facilities do not have to be built.

The cost of sharing plant and equipment among different biotechnology drugs is much higher because of the more stringent U.S. Food and Drug Administration (FDA) requirements governing the manufacture of biological products. Although the FDA regulates the

[1] Companies themselves often have difficulty estimating the cost of producing and selling specific products or services (216). New methods for assigning costs to different products have been proposed but are not fully diffused into company practice (92,93,94,95).

[2] The six firms are Marion Merrell Dow (1989-90), Merck (1988-90), Schering-Plough (1989-91), Syntex (1989-91), Upjohn (1988-90), and Eli Lilly (1987-89).

manufacture of all kinds of pharmaceuticals, the requirements for facilities that manufacture biological products are more stringent (41). The potential for contamination is greater with biological products than with synthetic compounds, and containment areas may be necessary. Although the FDA does not prohibit biotechnology firms from manufacturing more than one product in a facility, many companies elect to build a dedicated facility to manufacture biotechnology products because of the stringent requirements (186). One biotechnology executive recently submitted a statement in congressional hearings that a dedicated bulk biopharmaceutical facility would cost approximately $25 million (31).

The drugs approved in the period 1981-83 included only a very few biotechnology drugs, so the special manufacturing problems with these products were not present. Anecdotal evidence about costs of building production facilities for two drugs, atenolol (Tenormin™) and loracarbef (Lorabid™) provides some information on synthetic chemicals. A recent bulk pharmaceutical plant for Tenormin™, an antihypertension drug, cost $60 million to construct (382). Tenormin had 1990 world sales of approximately $1.2 billion and was the fifth highest selling drug worldwide in 1991 (385). Eli Lilly and Company announced a $65-million plant to manufacture Lorabid (383). Although Lorabid™ was approved in December 1991 and launched in 1992, Kidder Peabody analysts forecast annual sales of at least $500 million for this antibiotic (384), which would place Lorabid™ near the top 25 selling drugs in 1991 (385).

These high-volume drugs can be expected to have higher capital expenditures for manufacturing plant and equipment. OTA estimates the mean worldwide sales of the drugs approved between 1981-83 in the fifth year after product launch were $170 million (in 1990 dollars). The few big winners are accompanied by many drugs with low sales. For example, if 1 out of 10 drugs is large enough to require $60-million manufacturing facilities, and the other 9 out of 10 drugs require $20-million manufacturing facilities, the average capital expenditure would be under $25 million.

OTA took the above information as a basis for estimating the costs of constructing plant and equipment to manufacture 1981-83 drugs, We assumed such facilities would cost $25 million, expended equally over a 3-year period beginning 2 years before market launch and ending in the year of market launch approval. Because of the uncertainty associated with this estimate we examined the impact on the estimated returns on R&D of an average expenditure for plant and equipment of $35 million. (The results are presented in chapter 4.)

OTA's analysis of returns on R&D also included expenditures for capital facilities in other forms. The administrative and marketing cost estimates include charges for depreciation on facilities used in these functions. In addition, the cost of sales includes any charges for depreciation on manufacturing facilities in excess of the depreciation that would be charged for the $25-million facility. Also, manufacturers of drugs in finished form often buy their bulk chemicals from fine chemical producers. The cost of these materials to the pharmaceutical companies is included in pharmaceutical companies' financial statements as operating costs of goods sold. Thus, the estimate of cost of goods sold contains an implicit rental charge for the value of the manufacturing facilities used to produce bulk chemicals purchased from other producers. Therefore, if the capital expenditures on plant and equipment were in reality higher than $25 million, the extra costs would be at least partially captured in residual depreciation charges and cost of materials embedded in the cost-of-sales estimates.

Administrative Costs

Administrative costs are typically reported together with marketing costs in companies' annual financial statements. The marketing and administrative cost for the six firms was 33.6 percent of total sales in the years examined. One firm (Eli Lilly) reported over a 3-year period that 67 percent of marketing and administrative costs were for marketing. If this one firm is representative of the industry, administrative costs would be 11.1 percent of total sales. OTA used this estimate of administrative costs and assumed the percent would not vary over the life of the product. (A producer of generic drug products, Barr Laboratories, reported its annual general and administrative costs at 7.5 to 10.1 percent of sales in the period 1989-91.)

Marketing Costs

Marketing costs comprise promotion (advertising and detailing), sponsorship of symposia and other promotional events, and support functions such as market research. Between 1987 and 1990, in the six companies surveyed by OTA, 33.6 percent of sales were devoted to marketing and administrative costs. If Eli Lilly's cost structure is typical of the research-

intensive **industry,** then 22.5 percent of pharmaceutical companies' total sales are devoted to marketing.

Another way of examining the ratio is to begin with advertising expenses, which are reported by companies, and estimate the ratio of advertising to other marketing expenses from published sources. Baber and Kang reported the average ratio of advertising to total sales for 88 pharmaceutical companies was 6.9 percent between 1975 and 1987, and the ratio for 54 research-intensive pharmaceutical companies was 4.5 percent (26).[3] Among the six U.S.-owned companies examined by OTA the ratio of advertising to sales averaged 4.3 percent in 1989 and 1990. In 1989, advertising comprised 26 percent and detailing activities comprised 74 percent of total promotional expenses for ethical pharmaceuticals (73). These facts together imply total promotional expenditures comprise between roughly 17' and 26 percent of sales.

OTA assumed 22,5 percent of pharmaceutical companies' total sales are devoted to marketing. These expenditures vary over the life of a product, however, and can be expected to be high in the early years of marketing and relatively low after a product loses patent protection. Caves, Whinston and Hurwitz reported on originator brand promotion expenses in the year of patent expiration for a sample of 21 drugs that lost patent protection between 1982 and 1987. Promotion comprised 6.5 percent of total sales in the year of expiration (73). OTA therefore assumed marketing expenses would be 6.5 percent of sales in the years subsequent to patent expiration.

OTA assumed marketing expenses in the first year after product approval would be equal to total worldwide sales; in the second year, they would be equal to 50 percent of worldwide sales (159). In the 3rd to 9th year (when patents expire), OTA assumed marketing costs would be equal to the percent that equates total marketing costs over the product life cycle to 22.5 percent of total sales over the life cycle. This calculated percent was 40.6.

Inventory Costs and Working Capital

The cost of producing inventory was calculated by assuming the company would build up inventory in each year equal to 12.7 percent of sales in the year (the average ratio of inventory to sales in the six U. S.-owned companies examined by OTA). If inventories are valued at the cost of goods sold, this percent is equivalent to 4.8 months of sales held in inventory. As sales decline at the end of the product life cycle, inventories decline accordingly. Working capital to finance accounts receivable was also charged against revenues. Accounts receivable comprised 17.2 percent of sales in the six pharmaceutical firms. This amount was used to estimate the working capital required in each year. As sales decline at the end of the product life cycle, accounts receivable decline as well.

Cost of Ongoing R&D

Since the revenue curve for a typical NCE is based on the total sales for the molecular compound for all indications and formulations, it is appropriate to include ongoing R&D that takes place after FDA approval and marketing to support new indications, new dosage forms, or routes of administration. Additional research may also be needed to obtain marketing approval in other countries. OTA estimated the cash outlays for ongoing R&D at $31.7 million (in 1990 dollars) per NCE over the product life cycle. This estimate was made for OTA by Dr. Joseph DiMasi from information obtained in his survey of R&D costs (109). In that study, the 14 surveyed companies reported that over the period from 1970 to 1986, research on self-originated NCEs comprised 73.7 percent of all R&D; research on licensed-in NCEs comprised 10 percent of all R&D; and existing product research totaled 16.3 percent of all R&D. OTA assumed existing product research is allocated proportionately between self-originated NCEs and licensed-in NCEs. DiMasi and colleagues also estimated the cash outlays associated with producing a self-originated NCE were $127.2 million (in 1990 dollars). Ongoing R&D costs associated with this expenditure based on these figures would be $20.7 million. Spending increased over the study period, however, and DiMasi estimated the time between spending on proapproval R&D and postapproval R&D requires an adjustment of the ongoing R&D estimate to $31.7 million (106). OTA used this estimate in its analysis of returns on new drugs.

Alternative Approach to Measuring Manufacturing and Distribution Costs

Because the estimates of production and other costs are imprecise, OTA compared the results of the above analysis with production and distribution costs calculated using an alternative method. This second method

[3] Pharmaceutical companies were identified as publicly traded U.S. registered companies reporting standard industrial classification (SIC) code 2834 (pharmaceuticals) as their principal line of business. Research-intensive firms were a subsample of the pharmaceutical firms whose ratio of R&D to sales was 5 percent or greater.

Table G-I—Ratio of Generic Price[a] to Originator Price by Year Relative to Patent Expiration[b] (for 30 compounds whose patents expired 1984-87)

Year relative to patent expiration	–3	–2	-1	0	+0	+2	3
Ratio	0.49	0.46	0.41	0.38	0.39	0.37	0.32

a Generic price is the average nonoriginator price in year 3, or in year 4 if no generic sales were recorded in year 3.
b Average price weighted by originator drug's physical volume as measured by defined daily dose.

SOURCE: Office of Technology Assessment, 1993, based on data from S.W. Schondelmeyer, "Economic Impact of Multiple Source Competition on Originator Products," contract paper prepared for Office of Technology Assessment, December 1991,

uses information about the price of generic drugs to infer the cost of manufacture and distribution of originator products.

As several researchers have noted, when a large number of generic suppliers have entered a market, the average price of the generic version of a drug can be taken as an upper bound on the long-run marginal cost of producing and distributing the product and providing general and administrative services in the running of the company (73,161). The pressures of price competition will, with entry of new firms, drive generic producers to charge prices that just cover the cost required to stay in business. This cost includes the required return on investment, or cost of capital. Thus, a brand-name product markup over marginal production, distribution, and administrative cost cart be roughly estimated by the difference between the brand-name price and the generic price.

The ratio of generic to originator price serves as a proxy for production, distribution, administrative, inventory, and working capital costs. It also includes the costs of facilities and equipment used to produce the product. These costs are recognized in the generic price as an effective rental or lease payment for such facilities.[4]

Generic companies also spend some funds to market their products, and they incur substantial R&D costs which also must be covered in the price they charge.[5] However, marketing and R&D costs for originator products are likely to be much higher than for generic products; consequently, the generic price does not fully cover these components of cost.

Although few if any of the compounds approved between 1981 and 1983 have faced any generic competition to date, OTA did have access to data on the sales of 35 compounds that lost patent protection in the period 1984-87 (368). For 30 of these compounds,[6] OTA calculated the ratio of the generic price obtaining in the third year after patent expiration (measured in 1990 dollars) to the originator's price in each year, from 3 years prior to patent expiration to 3 years after patent expiration.[7] Table G-1 shows the ratio of generic price (or marginal cost) to originator's price in the 7 years surrounding patent expiration for the 30 drugs in the sample. As expected, the ratio of generic price (marginal cost) to originator price declines as time passes. These results are consistent with the widely observed rise in average originator's price immediately before and after patent expiration (see appendix F) (73,161,195,368).

To compare the cost estimates from financial statements with those derived from the generic price ratios, a ratio of cost to price is required for the entire product life cycle. OTA had no data on originators' transaction prices in the first 5 years of product life for NCEs approved in the 1981-83 period. A review of published wholesale list prices for these compounds suggests that after adjusting for inflation, prices tended to rise in real terms in the first few years after introduction. (See table G-2,) The simple average annual rate of increase in price over the first 4 years of

[4] Although generic firms may build and own their own factories, the price they charge for the product must reflect the amount they must pay their investors for the usc of the facility, This rental rate is implicit in the competitive price of the product and does not have to be explicitly estimated.

5 Three generic companies whose annual financial statements were examined by OTA incurred R&D costs of 5 to 6 percent of sales in 1990. In addition, marketing expenses by onc firm (that reported such expenses separately) amounted to 6.5 percent of sales, (36) the same as that estimated for originator firms in the year of patent expiration (73).

6 Five of the drugs had no generic competitors in 1990, the last year of data collection.

[7] The generic price is measured by the total revenue across all generic producers of the same drug divided by the estimated volume of defined daily doses (DDDs) sold. The originator's price is total originator's revenue divided by the physical volume sold (measured in DDDs). The overall ratio of generic price to originator price in each year was calculated by weighting each drug's ratio by the volume of DDDs sold.

Table G-2-Changes in List Price of New Chemical Entities Approved Between 1981 and 1983

NCE name	U.S. trade name	Approval year	Dosage form	Rate of change in real price[b]			
				Year 1-2	Year 2-3	Year 3-4	Year 4-5
albuterol	Proventil	1981	Inhaler, 90 mcgm	0.08	0.06	0.19	-0.03
alprazolam	Xanax	1981	Tab, 0.25mg, 100s	0.14	0.17	0.07	
alprostadil	Prostin VR	1981	Amp, 500 mcgm/1 ml, 5s	0.06	0.07		
amiloride	Midamor	1981	Tab, 5mg, 100s	-0.04	0.06	0.17	0,12
atenolol	Tenormin	1981	Tab, 50mg, 100s	0.08	0.00	0.15	
buprenorphine	Buprenex	1981	Amp, 0.3mg/1 ml, 10s				
captopril	Capoten	1981	Tab, 25mg, 100s	-0.04	-0.04	0.19	0.05
cefotaxime	Claforan	1981	Via, 1gm, 10s	-0.04	-0.04	-0.17	-0.03
ceruletide	Tymtran	1981	Amp, 2ml, 5s		0.06		
estramustine	Emcyt	1981	Cap, 140mg, 100s	*-0.04*			
flunisolide	Nasalide	1981	Sol, 0.25%, 25ml	*0.02*	0.09	0.09	
gemfibrozil	Lopid	1981	Cap, 300mg, 100s		0.14	0.20	0.07
halazepam	Paxipam	1981	Tab, 20mg, 100s	0.24	0.06	0.29	-0.03
ketoconazole	Nizoral	1981	Tab, 60s				
latomoxef	Moxam	1981	Via, 1gm/10ml, 10s	*-0.04*	-0.04		
mezlocillin	Mezlin	1981	Via, 1gm/10ml, 10s		-0.03	-0.03	
nifedipine	Procardia	1981	Cap, 10mg, 100s		0.05	0.07	0.07
piperacillin	Pipracil	1981	Via, 2gm		-0.04	-0.03	-0.03
sucralfate	Carafate	1981	Tab, 100s		0.06	0.07	
temazepam	Restoril	1981	Cap, 15mg, 25s	0.10	0.10	0.06	
trazodone	Desyrel	1981	Tab, 50mg, 100s		0.22	0.11	
verapamil	Isoptin	1981	Tab, 80mg, 100s	*-0.04*			
aciclovir	Zovirax	1982	Oin, 5%, 15gm tube		0.07		
azlocillin	Azlin	1982	Via, 2gm/30ml, 10s			-0.03	
cefoperazone	Cefobid	1982	Via, 1gm				
cellulose	Calcibind	1982	Pow, 2.5gm, 90s			0.15	
ciclopirox	Loprox	1982	Cream, 1%, 15gm,tube		0.05		
diflunisal	Dolobid	1982	Tab, 250mg, 60s, uni	0.07	0.13	0.03	
diltiazem	Cardizem	1982	Tab, 30mg, 100s	-0.04	0.06	0.06	
econazole	Spectazole	1982	Cream, 1%, 15gm, tube		0.01		
etomidate	Amidate	1982	Syr, 2mg/1 ml, 20gx1				
gonadorelin	Factrel	1982	Pow, 100mcgm	0.20	0.07		
guanabenz	Wytensin	1982	Tab, 4mg, 100s	0.06	0.03	0.07	
guanadrel	Hylorel	1982	Tab, 10mg, 100s		0.12	0.07	
isotretinoin	Accutane	1982	Cap, 10mg, 100s		0.07		
malathion	Prioderm	1982	Lotion, 20oz	-0.04	0.10		
niclosamide	Niclocide	1982	Tab, 500mg, 4s		0.07		
pindolol	Visken	1982	Tab, 5mg, 100s		0.22		
piroxicam	Feldene	1982	Cap, 10mg, 100s		0.08	0.09	0.09
praziquantel	Biltricide	1982	Tab, 600mg, 6s		0.07	0.07	
sodium phosphate		1982					
streptozocin	Zanosar	1982	Via, 1gm	-0.04	-0.03	0.04	
triazolam	Halcion	1982	Tab, 0.25mg, 100s		0.20	0.09	
acetohydroxamic	Lithostat	1983	Tab, 250mg, 120s				
atracurium	Tracrium	1983	Amp, 10mg/5ml, 10s				
bentriomide	Chymex	1983	Sol, 500mg, 7.5ml				
bumetanide	Bumex	1983	Amp, 0.25mg/2ml, 10s		-0.03		
ceftizoxime	Cefizox	1983	Via, 1gm/28ml, 1s				
cefuroxime	Zinacef	1983	Via, 750mg/1 ml				
chenodiol	Chenix	1983	Tab, 250mg, 100s		-0.03		

(Continued on next page)

Table G-2—Changes in List Price of New Chemical Entities Approved Between 1981 and 1983--(Continued)

NCE name	U.S. trade name	Approval year	Dosage form	Rate of change in real price[b] Year 1-2	Year 2-3	Year 3-4	Year 4-5
ciclosporin	Sandimmune	1983	Amp, IV, 50mg/5ml, 1s				
indapamide	Lozol	1983	Tab, 2.5mg, 100s		0.09		
netilmicin	Netromycin	1983	Syr, 150mg/1.5ml, 10s	-0.27			
ranitidine	Zantac	1983	Tab, 60s				

a Real prices calculated using GNP implicit price deflator; prices are retail or wholesale prices given in *Drug Topics Redbook*.
b Entries are blank when data are unavailable.
KEY: Amp—Ampoule; Cap—Capsule, IV—intravenous; Oin—Ointment; Pow-Powder; Sol-Solution; Syr—Syringe; Tab-Tablet; Via—Vial.
SOURCE: Office of Technology Assessment, 1993, based on data from *Drug Topics Redbook* (Montvale, NJ: Medical Economics Company, Inc., 1981-86).

product life was 5,5 percent for compounds in the sample for which list prices were available. OTA assumed this rate of increase in prices would continue throughout the first 5 years of product life, culminating in a ratio in year 6 of 0.49 (see table G-l).

For the last years of the product life cycle (4 and more years after patent expiration), OTA assumed originator prices would stabilize and the observed ratio (0.32) in the third year of patent life would hold in subsequent years.

This approach to estimating the marginal cost of the 1981-83 compounds (excluding marketing and R&D) is itself imprecise. The ratios are based on an entirely different set of drugs from the ones whose net returns are being analyzed. The approach assumes the average inflation-adjusted markup on a compound depends only on its age relative to patent expiration; drugs approved between 1981 and 1983 are assumed to have markups over cost that mirror those for drugs whose patents expired in 1984-87. Because this assumption is arbitrary, OTA did not use the method as a primary estimation procedure; rather, the cost estimates are merely intended to corroborate the estimates taken from companies' financial reports.

Table G-3 compares costs of production, distribution, and administration as a percent of sales in each year following market approval under the two methods of cost estimation. The marginal cost estimate, which represents an upper bound on actual costs, is higher than the financial statement estimates in most years. It is much higher (by up to 13 percentage points) in the early years. The marginal cost estimate includes both marketing costs for generic companies, which may be as much as 6 percent of sales, and an implicit rental cost of facilities and equipment, while the financial statement estimates given in the table do not include these costs. It also includes the cost of ongoing R&D for generic companies, which comprise approximately 5 to 6 percent of sales. If marketing and R&D costs were removed from the generic price ratio (at an assumed rate of 11 percent of sales), the resulting generic price ratio would be lower than the costs based on financial statements in almost every year. This comparison suggests cost estimates based on recent financial statements of research-intensive pharmaceutical firms do not underestimate actual costs over the product life cycle.

Table **G-3—Cost of Production, Distribution, Administration, Working Capital and Inventories as Percent of Sales Under Different Estimation Methods**

Number of years after approval	Financial statement estimates	Generic price ratio[b] (marginal cost)
1	60.8%	62.8%
2	44.5	57.0
3	47.8	57.0
4	41.5	54.3
5	41.1	51.7
6	39.6	49.1
7	39.0	45.7
8	41.4	41.0
9	30.0	38.5
10	33.4	39.0
11	34.2	37.2
12	34.1	32.1
13	34.4	32.1
14	34.4	32.1
15	34.4	32.1
16	34.3	32.1
17	28.7	32.1
18	28.4	32.1
19	28.1	32.1
20	27.6	32.1

a This estimate *excludes* expenditures for capital facilities and equipment, marketing, and ongoing R&D costs.
b This ratio *includes* implicit costs of rental of capital facilities and equipment, ongoing R&D and marketing costs of generic producers, and return to investors.

SOURCE: Office of Technology Assessment, 1993.