Appendix F

Summary of Methods Used to Analyze Trends in Postpatent Revenues

The Office of Technology Assessment (OTA) contracted with Dr. Stephen Schondelmeyer to report on trends in sales revenue and unit sales volume for molecular compounds that lost patent exclusivity during the 4-year interval 1984-87 (368). The period 1984-87 was chosen because the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) significantly reduced the barriers to market entry for generic manufacturers by allowing the U.S. Food and Drug Administration (FDA) to expedite the approval process for generic versions of drugs already proved safe and effective. Data were provided on sales of the sampled compounds from 1980 to 1990.

Dr. Schondelmeyers report to OTA is based on data from the IMS America, Inc. MIDAS system using the United States Drugstore and United States Hospital database. That database does not include sales made directly to mail-order distributors, health maintenance organizations, or Federal Government health purchasers (such as the U.S. Department of Veterans Affairs and the military.) In 1986, IMS America claimed the database reflected 98 percent of ethical pharmaceutical sales in the United States (368), but this share may be declining as mail-order pharmacies become more important.

Sample Selection

OTA supplied the contractor with a list of 83 pharmaceutical compounds which came off patent in the period 1984-87. This list was compiled from sources that included the FDA (262), trade publications and market research surveys. Products approved for over-the-counter sale during the period of study were excluded from the sample. Combination products were also excluded, except for two (methyldopa with hydrochlorothiazide and triamcinolone acetonide with nystatin). [1]

Drug products that would not be marketed in significant quantity through community-based pharmacies were also removed from the sample.[2] These included injectable, infusible, and diagnostic drug products. Injectable and infusible drugs make up a negligible part of the outpatient market but a larger proportion of the hospital market. Informal discussions with hospital pharmacists in a large voluntary hospital chain suggest injectable and infusible drugs constitute approximately 60 percent of dollar purchases of inpatient drugs.

After eliminating products not meeting the criteria for inclusion, 45 products were in the sample. The drugs on OTA's list also were compared with a drugstore database held by Purdue University (based on IMS data), and compounds with no recorded sales in any of the study years were eliminated. After this round, 41 drugs remained in the sample (see table F-l).

Further analysis of the IMS data showed some products with substantial generic sales in years prior to the assumed patent expiration date. We contacted the company marketing the brand-name product and also referred to a summary of patent issue dates produced in 1988 by the Pharmaceutical Manufacturers Associations (PMA) (322). Four products were removed from the *list* when the true patent expiration year was found to be earlier than the year obtained from the FDA. (These compounds are listed with a footnote in table F-l.) Two additional drugs (enflurane and dimethyl sulfoxide) met the selection criteria as noninjectable, noncombination drug products but were dropped from

[1] For these two products, only the combination products with specific ingredients identified were included.

[2] At the time the sample of drugs was selected, the contractor believed that data available from IMS included only drugstore sales. IMS America ultimately provided the contractor with sales data for both drug stores and hospitals.

the analysis, because they are used almost exclusively in hospitals. Enflurane is a general anesthetic and dimethyl sulfoxide is a urinary tract diagnostic aid. Table F-1 shows the final list of 35 products included in OTA's analysis.

The patent issue dates compiled by the PMA also revealed a number of discrepancies with the FDA patent expiration dates. Only 13 of the 35 drugs showed no discrepancy between the FDA and PMA sources. Of the remaining 22 compounds, 18 had PMA patent expiration dates that were earlier than the FDA patent expiration date. Choosing a later patent expiration date makes the rate of decline of originator revenues immediately following expiration look higher. Therefore, to be conservative, OTA took the FDA date in these 18 cases.

In the remaining four cases, the earliest PMA patent expiration date was either the same or earlier than the FDA date, but the PMA source showed a second patent that expired after the FDA year. (The earliest patent typically covers the compound, while subsequent patents often involve process or uses.) There were no generic sales in the study years following the FDA patent expiration date for two of the four drugs. OTA chose the FDA patent expiration date as the year of patent expiration in all of these four cases.

Data Analysis

The contractor provided OTA with a report containing unit and dollar sales for each compound in the sample. Because a drug may be produced in different strengths, dosage forms and package sizes, the contractor constructed a standardized measure of unit sales (368). This measure of sales volume, the defined daily dose (DDD), is based on the typical daily dose of a given drug product for an adult patient being treated for the drug's primary indication.

Dollar and unit sales data were compiled for the compound as a whole across all its dosage forms and strengths. We selected this orientation to examining generic competition because the returns to R&D depend on the entire history of the compound, including the exclusive opportunity to develop new dosage forms before the patents on the original compound expire.[3] Such product extensions bring with them 3 additional years of exclusive marketing rights from the FDA.[4]

Table F-1—Noninfusible Noninjectable New Chemical Entities Losing Patent Protection, 1984-87

Drug entity	Year of patent expiration
acetohexamide	1984
amiloride	1984
baclofen	1986
beclomethasone	1984
carbamazepine	1986
cefadroxil	1987
cephalexin	1987
cephradine	1986
clindamycin	1987
clonidine	1986
clorazepate	1987
danazol	1984
desipramine	1986
diazepam	1985
dimethyl sulfoxide[a]	1987
disopyramide	1985
doxepin	1986
enflurane[a]	1986
fluocinonide[b]	1986
flurazepam	1985
haloperidol	1986
lactulose	1986
lorazepam	1985
maprotiline	1986
meclofenamic acid	1985
mesoridazine	1985
methyldopa	1985
methyldopa hctz	1984
metoclopramide	1985
molindone	1987
oxazepam	1984
perphenazine	1986
propranolol	1985
sucralfate	1986
temazepam	1985
thiothixene	1984
tolazamide[b]	1985
trazodone	1985
triamcinolone[b]	
trifluoperazine[b]	1985
verapamil	1986

a Passed selection criteria as noninfusible, noninjectable, noncombination drug products, but not typically used in an outpatient setting; removed from analysis.
b patent expiration year found to be earlier than year obtained from the FDA; removed from analysis.

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

[3] Under this approach, the costs of R&D required to put the extended product on the market must also be included in an analysis of the returns to R&D. OTA included an estimate of such costs in its analysis of returns to R&D.

[4] The additional years of effective patent life obtained from new dosage forms were not reflected in OTA's estimate of effective patent life. That estimate is based on the effective patent life for the original compound.

Sales were reported to OTA in current dollars, but OTA converted them to constant 1990 dollars using the GNP implicit price deflator. OTA had 11 years of data which allowed examination of sales over a 14-year period relative to the year of patent expiration. Data on each compound were aligned according to the year of patent expiration. For example, sales in the first year after patent expiration for compounds whose patents expired in 1984 were those reported in 1985, whereas sales in the first year after patent expiration for compounds whose patents expired in 1987 were those reported in 1988. Thus, 1988 inflation-adjusted sales for the 1987 drugs were combined with 1985 inflation-adjusted sales of the 1984 drugs to obtain inflation-adjusted sales 1 year after patent expiration for the entire sample.

Data for the entire sample of 35 drugs were available from 4 years prior to patent expiration to 3 years after expiration. For earlier and later years, data were available for only a part of the sample. For example, data on dollar and unit sales in the sixth year after patent expiration were available for only eight drugs: those whose patents expired in 1984. The 6-year postpatent estimate is based on 1990 sales and volume data for these eight drugs. Also, 7 of the 35 drugs received FDA marketing approval after 1980. A drug was included in each year's analysis only when the product was marketed for the complete year.

Summary of Results

Table F-2 shows the mean sales revenue (in constant 1990 dollars), and unit sales of originator products in each year relative to the year of patent expiration (year

Table F-2--Originator Sales of Compounds Losing Patent Protection, 1984-87

Year relative to patent expiration[a]	Sample size	Revenue per drug[b] (standard deviation)	Unit volume per drug[c] (standard deviation)
-7	5	$63,051 (79,645)	44,435 (45,950)
-6	14	41,887 (52,518)	60,346 (61,989)
-5	22	63,110 (86,663)	129,691 (195,887)
-4	32	60,258 (78,034)	118,697 (166,164)
-3	34	62,246 (77,934)	115,621 (156,440)
-2	35	68,194 (83,229)	115,823 (152,824)
-1	35	77,661 (91,620)	115,710 (143,258)
0	35	79,657 (84,010)	108,791 (126,585)
+1	35	69,810 (61,392)	90,513 (95,021)
+2	35	67,239 (66,448)	83,098 (98,475)
+3	35	66,012 (79,686)	73,771 (100,104)
+4	30	63,570 (94,340)	71,105 (108,036)
+5	18	50,832 (52,217)	49,181 (48,448)
+6	8	40,588 (59,995)	38,023 (51,406)

a Year 0 is the year of patent expiration.
b Measured in thousands, constant 1990 dollars.
c Measured in defined daily dose, in thousands. See text for explanation.

SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, "Economic Impact of Multiple Source {competition on Originator Products, "contract paper prepared for Office of Technology Assessment, U.S. Congress, December 1991.

O). Note that in the early and late years, only a subsample of drugs is included in the estimates. Year-to-year changes in revenues, shown later in this appendix, were calculated only for drugs for which data were available in both years.

The originator brand's market share in each year relative to the year of patent expiration is shown in table F-3. Originator products maintained almost 85 percent of the total market share (in dollars) as long as 6 years after patent expiration, but the originator product's market share in unit volume declined to 50 percent within 4 years of patent loss.

OTA examined changes in originators' dollar and unit sales over the years immediately preceding and following the year of patient expiration (figures F-1 and F-2.) Average year-to-year changes in revenues and unit sales were calculated only for drugs for which data were available in both years. Between the second year prior to patent expiration and the third year after patent expiration, all 35 drugs were in the sample. In contrast, only eight drugs were used to calculate the

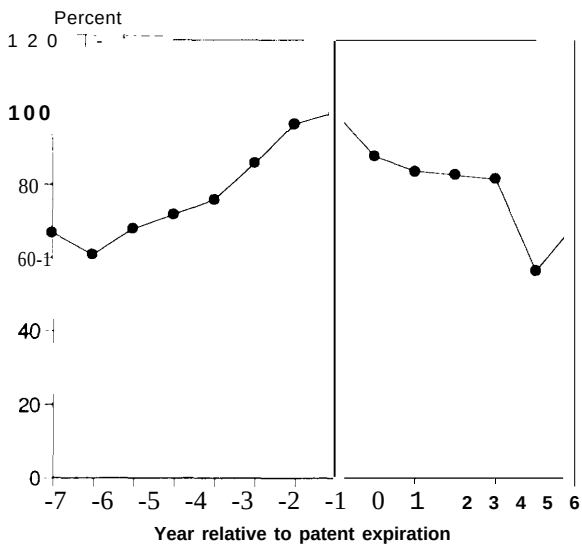
Table F-3—Originator's Market Share

Year	Dollar Sales	Unit Sales[b]
-7	100"/0	100%
-6	99	100
-5	99	100
-4	99	100
-3	99	100
-2	99	100
-1	99	100
0	95	94
+1	86	73
+2	84	6 5
+3	84	57
+4	85	51
+5	83	44
+6	85	62

a 'fear o is the year of patent expiration.
b Unit sales are measured in defined daily dose.

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

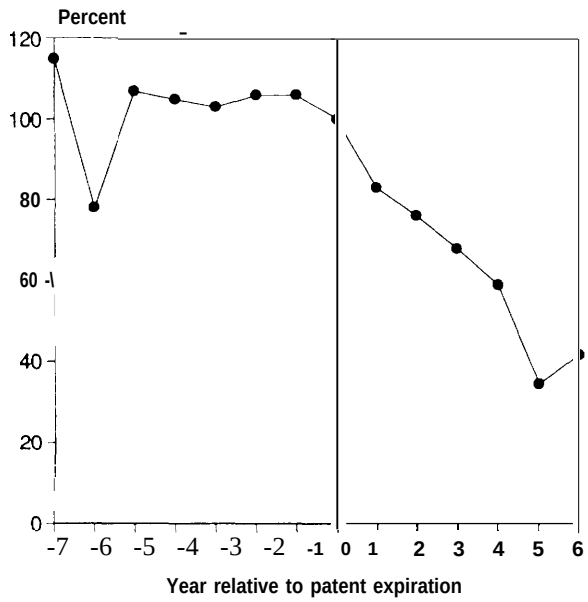
Figure F-l—Originator Dollar Sales as Percent of Originator Dollar Sales[a] in Year of Patent Expiration for Drugs Losing Patent Protection, 1984-87



KEY: Year O is year of patent expiration.
a Based on 1990 dollars.

SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, 'Economic Impact of Multiple Source Competition on Originator Products,' cent ract paper prepared for Office of Technology Assessment, December 1991.

Figure F-2-Originator Unit Sales as Percent of Originator Unit Sales in Year of Patent Expiration for Drugs Losing Patent Protection, 1984-87



KEY: Year O is year of patent expiration.

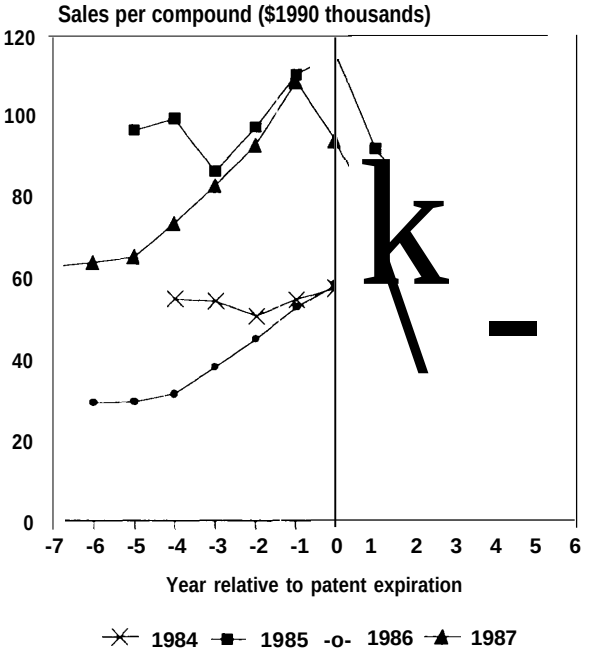
SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, 'Economic Impact of Multiple Source Competition on Originator Products,' contract paper prepared for Office of Technology Assessment, December 1991.

average percentage sales loss between the fifth and sixth year after patent loss.

The sharp decline experienced in year +5 revenue, as shown in figure F-2, is due primarily to the loss of data on verapamil, which came off-patent in 1986 and had 1990 revenue approaching $500 million. The originator market for verapamil actually grew after patent expiration because of the introduction by its manufacturer of a new sustained release dosage form shortly before its patent expired. Its loss to the sample in years 5 and 6 accounts for the substantial recorded decline in originator revenues in the figure.

Data on the history of revenues and unit sales volume for drugs coming off patent in each of the study years are presented in figures F-3 and F-4. Substantial differences were recorded in the pattern of revenue and unit volume loss across these subsamples, although originator sales and unit volume declined in all but one cohort of drugs. The sales volume for the 1986 cohort actually increased after patent loss. This was primarily due to verapamil's product line extension.

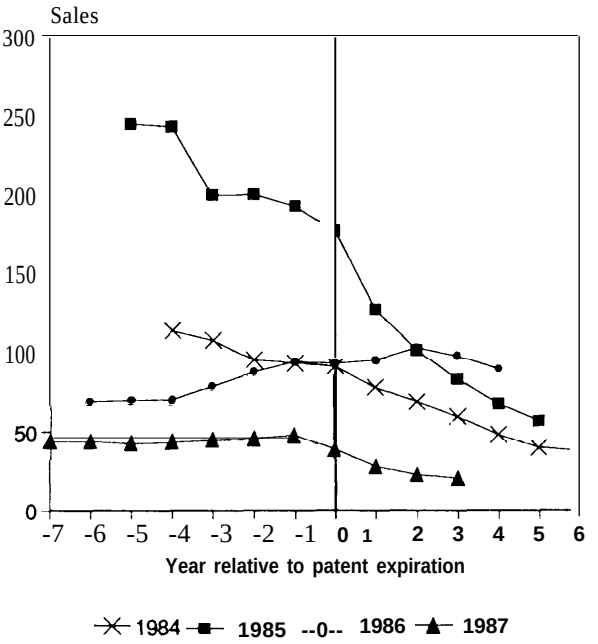
Figure F-3—Originator Dollar Sales for Drugs Losing Protection, 1984-87



KEY: Year O is year of patent expiration.

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

Figure F-4-Originator Unit Sales[a] for Drugs Losing Protection, 1984-87 ($ 1990)



KEY: Year O is year of patent expiration.

a Unit sales are measured in defined daily dose.

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

Some reviewers of OTA's draft report argued verapamil is an unusual case, both because it had anew sustained release form and because the indications for the drug were expanding over the period. Consequently, these reviewers believed OTA should remove verapamil from the sample of drugs.

The presence of verapamil in the sample of drugs does, indeed, have a large impact on the estimated rate of decline in originator sales following patent expiration. Verapamil had the highest inflation-adjusted dollar sales of all drugs in the sample by the third year after patent expiration, and its sales revenue inconstant dollars grew over the period.

That there is wide variation among different compounds in their sales history and product life cycle is undisputed. In that sense, every drug is unusual. Manufacturers do depend on a few "big winners" to carry the fixed costs of R&D and marketing necessary to develop and sell drugs in today's market (159). OTA's analysis is at the industry level, however, and an accurate representation of the pattern of loss of

revenues after patent expiration would be impossible if the big winners were excluded from the analysis. (The industry would appear to be losing great sums if the high selling drugs were removed.)

The practice of managing patent life by timing the introduction of new dosage forms is becoming more common, not less common, in recent years, as new drug delivery systems have become available. At least 4 of the 35 drugs in the sample had product line extensions that lengthened their exclusive marketing rights beyond the year in which the patent governing the compound itself expired. The extraordinary sales growth of verapamil's originator brand after its patent expired would probably have been substantially dampened without the extended release form.

One reviewer of OTA's draft report pointed out that one compound, chlorpropamide, whose patent expired in 1985 and whose 1985 inflation-adjusted sales were higher than all but four of the drugs in the sample, was not included in OTA's ultimate sample, even though it meets the inclusion criteria. Upon re-reviewing the selection process OTA discovered this drug had been eliminated from the sample because preliminary analysis of Purdue University's database had indicated many generic companies were manufacturing the product as early as 1981. This finding had suggested to us that the patent was not effectively barring generic competition and we therefore excluded it from the sample. As part of the re-review of this issue, we obtained rough estimates of sales of the originator's brand-name product, Diabenese™,and generic copies™, which showed the generic sales in 1985 of chlorpropamide, were very small. Therefore, excluding Diabenese from the sample was probably a mistake.

Although OTA does not have access to the full history of sales of Diabenese and its generic competitors, we did obtain an estimate of its sales in 1985 and 1991. We assumed sales would decline at a constant percentage rate between 1985 and 1991. Using the resulting sales estimates for Diabenese, we recalculated the rate of decline in originators' revenues in the years after patent expiration. Table F-4 shows that the year-to-year decline in revenues after patents expire changes very little when Diabenese is included. Because OTA did not have access to the actual sales data for all years of the study, we did not recalculate any of the other tables presented in this appendix, but we did use the revised estimates of dollar sales declines in the analysis of returns on R&D.

Table F-4—Decline in Originator Dollar Sales With and Without Diabenese™ in Sample

Year relative to patent expiration[a]	Rate of change excluding Diabenese (percent)	Rate of change including Diabenese (percent)
0 to +1	–12.0%	–1 2.90/.
+1 to +2	–4.0	–4.6
+2 to +3	-2.0	-2.7
+3 to +4	-5.0	-5.5
+4 to +5	-5.0	-5.3
+5 to +6	+3.0	+3.4

[a] year 0 is the year of patent expiration.

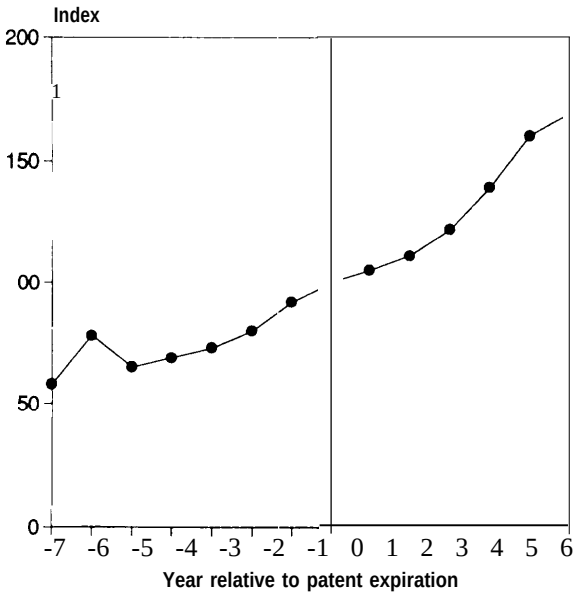
SOURCE: Office of Technology Assessment, 1993.

The relatively slow postpatent decline in dollar sales of originator brands is surprising to many observers of the industry, because the impact of generic competition on the sales of some drugs and on the companies that manufacture them can be severe. OTA's analysis begins with the point at which the patent governing manufacture of the compound in its original form expires, not the point at which generic products enter the market. The entry of generics can be delayed by: 1) FDA's subsequent award of market exclusivity for follow-on products (as in the extended release example); 2) delays in FDA approval of generic copies of brand-name drugs; or 3) technical or market factors that discourage generic companies from entering the market at all. Drugs with small markets, or for which bioequivalence is difficult to achieve or demonstrate, may never have a generic competitor.

Another factor slowing down the decline in revenues is a steep increase in the price of the originator drug after patent expiration. OTA developed a price index for originator products using average sales per DDD as a proxy. The average price of the originator product increased steadily throughout most of the period (figure F-5). It increased 69 percent in constant dollars in the 6 years after patent expiration. At the same time, the ratio of the average price of generic products to originator products decreased rapidly over the course of the study period (figure F-6). Four years after patent expiration, the generic price was just 20 percent of the originator price.

Manufacturers continue to increase the real price of their drugs as their share of the market in unit volume falls. The real price increases dampen the rapid decline in unit sales that follows generic competition. Even with a very large price discrepancy between generic

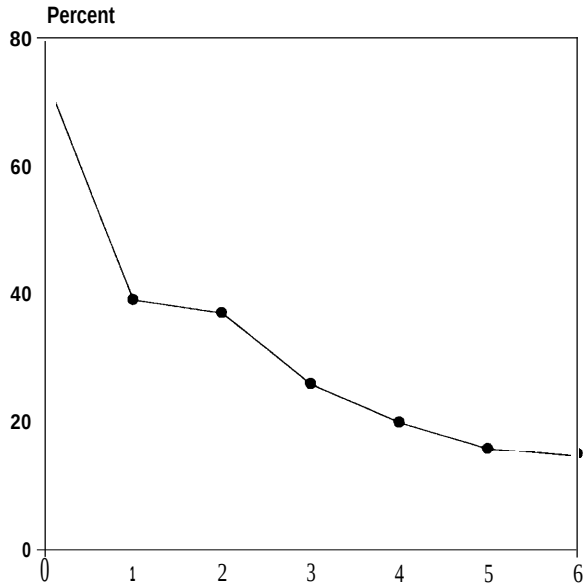
Figure F-5-Price Index for Originator Drugs[a] ($ 1990)



KEY: DDD = defined daily dose; Year O is year of patent expiration.
a Price is measured as average revenue (revenue/DDD).

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

Figure F-6—Non-originator Price as a Percent of Originator Price[a] ($ 1990)



a Average revenue ($ Sales/DDD), of nonoriginator drugs divided by average revenue of originator drugs.

SOURCE: Office of Technology Assessment, 1993, based on S.W. Schondelmeyer, 'Economic Impact *of* Multiple Source Competition on Originator ProductS,'contract paper prepared for Office of Technology Assessment, December 1991.

product prices and the originator price, however, the originator product still maintains roughly a 40-percent market share in physical units 5 years after the patent expires.

OTA Estimate of Decline in Originator Sales Revenue

The data shown in figure F-1 are the backbone of the estimate of the year-to-year rate of decline in dollar sales to both hospitals and drugstores after patent expiration. Because the sample of drugs did not include injectable and infusible products, however, the rate must be adjusted for the probable impact of these hospital products on the rate of loss of sales.

Generic substitution is much more common in hospitals, where strong formularies and centralized pharmacies can control prescribing and dispensing more thoroughly, and where the incentives are strong to purchase the least expensive version of a drug for hospitalized patients.

OTA estimates about 60 percent of dollar sales to hospitals are for injectable and infusible products. About 23 percent of all ethical pharmaceutical sales are to hospitals, which would imply that about 14 percent of sales overall are for these products. But a proportion of sales to hospitals are made through hospitals' outpatient pharmacies, which have no incentives to encourage doctors to prescribe generics, so 14 percent is an overestimate of the size of the injectable-infusible market.[5] Nevertheless, OTA assumed 14 percent of total sales are for these hospital products. OTA also assumed that dollar sales of these products to hospitals

5 About 2.4 percent of the market is made up of staff-model health maintenance organizations (HMO), which probably switch to generics much faster than the general community pharmacy market once generics are available. The overestimate of the injectable and infusible market compensates to an unknown degree for the failure of the IMS data to account for sales to these kinds of HMOs.

would decline at 50 percent per year from the year in which the patent expires. Table F-5 shows the resulting estimates of year-to-year changes in sales relative to the year of patent expiration. The year-to-year rates of change in the fourth column of table F-4 were used in OTA's analysis of the returns to R&D for the 1981-83 introductions of new chemical entities outlined in chapter 4.

Table F-5-Change in Originator Brand Revenues for Drugs Losing Patent Protection, 1984-87

Year relative to patent expiration[a]	Rate of change excluding injectable and infusible drugs[b] (percent)	Rate of change in injectable and infusible drugs[c] (percent)	Blended rate of change[d] (percent)	Rate of change in OTA's analysis[e] (percent)
-7 to -6	1.70/0	1.7%	1.7%	1.7%
-6 to -5	4.0	4.0	4.0	4.0
-5 to -4	6.6	6.6	6.6	6.6
-4 to -3	8.2	85.2	8.2	8.2
-3 to -2	12.7	12.7	12.7	12.7
–2 to –1	13.9	13.9	13.9	13.9
–1 to 0	2.6	2.6	2.6	2.6
0 to +1	-12.9	-50.0	-18.1	-18.0
+1 to +2	-4.6	-50.0	-8.5	-8.5
+2 to +3	-2.7	-50.0	--4.9	-6.0
+3 to +4	-5.5	-50.0	--6.6	-6.0
+4 to +5	-5.3	-50.0	-5.9	-5.0
+5 to +6	+3.4	-50.0	+3.1	-5.0

a year 0 is the year of patent expiration.
b Rates based on figure F-5 and sources therein.
C OTA assumed the rate of growth would be the same as with other drugs until the year of patent expiration, when revenues would decline by 50 percent per year,
d Injectable and infusible drugs were assumed to make up 14 percent of the market in Year 0.
e See chapter 4 for OTA's analysis of returns from R&D on drugs first introduced to the U.S. market in 1981-83.

SOURCE: Office of Technology Assessment, 1993.