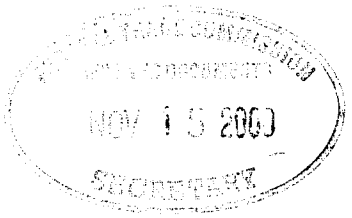
UNITED STATES OF AMERICA
BEFORE FEDERAL TRADE COMMISSION



In the Matter of HOECHST MARION ROUSSEL, INC., a corporation, CARDERM CAPITAL L.P., a limited partnership, and ANDRX CORPORATION, a corporation.	Docket No. 9293

To: The Honorable D. Michael Chappell
Administrative Law Judge

COMPLAINT COUNSEL'S MOTION FOR OFFICIAL NOTICE

Complaint counsel respectfully requests that Your Honor take official notice of the facts set forth below. Rule 3.43(d) of the Commission's Rules of Practice provides that the Administrative Law Judges and the Commission may take official notice of material facts that do not appear in evidence of the record, so long as the other party is given the opportunity to disprove such noticed facts upon a timely motion. 16 C.F. R. § 3.43(d). The concept of official notice is akin to that of judicial notice, provided for under Rule 201 of the Federal Rules of Evidence, but courts consistently have recognized that administrative agencies' ability to take official notice is even broader than the courts' ability to take judicial notice.[1]

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[1] *See generally* Kenneth C. Davis and Richard J. Pierce, Jr., II *Administrative Law Treatise* (3d ed. 1994) §§ 10.5 & 10.6 (discussing cases and observing that administrative agencies operating under the Administrative Procedures Act enjoy broader discretion to take notice of contested material facts than do courts operating under the Federal Rules of Evidence).

Administrative Law Judges at the Federal Trade Commission, as well as the Commission itself, have frequently relieved the parties in administrative adjudication of the duty to present formal evidence of certain facts by taking official notice of those facts. For example Administrative Law Judges and the Commission haven taken official notice of, and relied upon, extra-record facts derived from government agency studies and publications,[2] government guidelines and regulations,[3] government records,[4] Congressional reports,[5] and dictionaries.[6] Official notice is particularly appropriate when notice is being sought for so-called "legislative

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[2] *Beauty-Style Modernizers, Inc.*, 83 F.T.C. 1761, 1779 (1974) (taking official notice of a Federal Reserve Board publication).

[3] *Skylark Originals, Inc.*, 80 F.T.C. 337, 350 (1972) (taking official notice of Federal Trade Commission guidelines); *Marcor, Inc.*, 90 F.T.C. 183, 185 (1977) (taking official notice of a change in a Federal Reserve Board regulation).

[4] *Avnet, Inc.*, 82 F.T.C. 391, 484 n.31 (1973) (taking official notice of U.S. census data).

[5] *Rueben H. Donnelley Corp.*, FTC Dkt. No. 9079, Order Admitting Congressional Report as an Exhibit, November 15, 1978 (ALJ Timony) (taking official notice of four findings taken from a report of the Committee on Government Operations of the United States House of Representatives on Airline Deregulation and Aviation Safety), *citing Stasiukevich v. Nicholls*, 168 F.2d 474, 479 (1st Cir. 1948) ("The official report of a legislative or congressional committee is admissible in evidence in a judicial proceeding, as an exception to the hearsay rule, where the report, within the scope of the subject matter delegated to the committee for investigation, contains findings of fact on a matter which is at issue in the judicial proceeding. Indeed, the court could properly take judicial notice of the report, without its formal introduction into evidence.")

[6] *See e.g., Thompson Medical Co., Inc.*, 104 F.T.C. 648, 809-10 (1984) (taking official notice of the definition of "aspirin" found in various dictionaries). *But see Bristol-Myers Co.*, 95 F.T.C. 279 (1980) (Commission order denying respondent's motion that the Commission take official notice of selected newspaper reports).

facts," that is, facts that do not concern the immediate parties "but are general facts that help the tribunal decide questions of law and policy and discretion."[7]

Complaint counsel seek to have Your Honor take official notice of excerpts from a number of government agency publications, studies, regulations, and guidelines akin to the type of documents from which the Commission has frequently taken official notice. These documents are:

1. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998 ("CBO Study).

2. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "CDER 1998 Report to the Nation: Improving Public Health Through Drugs," 1998 ("CDER Report").

3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Fact Book 1997," 1997 ("CDER Fact Book").

4. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "CDER Handbook," revised March 16, 1998 ("CDER Handbook").

5. National Institutes of Health, National Heart, Lung, and Blood Institute, "The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," November 1997 ("JNC 6 Report").

6. Congress of the United States, Office of Technology Assessment, "Pharmaceutical R&D: Costs, Risks and Rewards," February 1993 ("OTA Study").

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[7] Davis and Pierce, Jr., II *Administrative Law Treatise* at §§ 10.5 p. 141 (contrasting "legislative facts" with "adjudicative facts," which "usually answer the questions of who did what, where, when, how, why, with what motive or intent"). *See also United States v. Gould,* 536 F.2d 216, 220 (8th Cir. 1976) ("Legislative facts are established truths, facts or pronouncements that do not change from case to case but apply universally, while adjudicative facts are those developed in a particular case.").

7. Health and Human Services, Food and Drug Administration, Proposed Rule for "180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications," 64 Fed. Reg. 42,873 (1999) (to be codified at 21 C.F.R. pt. 314) (proposed Aug. 6, 1999) ("FDA Proposed Rule").

Each of these documents is reliable on its face. The Congressional Budget Office study was conducted at the request of the Chairman of the Senate Committee on the Budget. As set forth in the CBO Study's preface, the study relies upon data and information provided by the Food and Drug Administration, the Patent and Trademark Office, the Health Care Finance Administration, and a variety of industry experts, and the study was peer reviewed by outside economics professors from MIT, Stanford, and Harvard prior to its publication. Additionally, both Hoechst Marion Roussel's economic expert, Dr. David T. Scheffman, and complaint counsel's economic expert, Dr. Richard G. Frank, rely upon and cite to the CBO Study in their expert reports submitted in this matter.

The CDER Report, CDER Fact Book, and CDER Handbook are issued by the Food and Drug Administration's Center for Drug Evaluation and Research ("CDER"). The CDER is the division within the Food and Drug Administration that evaluates new drugs for safety and effectiveness before they can be sold to the public, monitors the use of drugs for unexpected health risks, monitors drug information and advertising to ensure accurate and complete information is disseminated about approved drugs, sets the standards for drug quality and manufacturing processes, and conducts applied laboratory research and testing.

The JNC 6 Report is issued by the National Institutes of Health to provide guidance to primary care clinicians in the prevention, detection, evaluation, and treatment of high blood pressure. It encompasses the efforts of literally hundreds of physicians from all types of practices

(e.g., private, public, university-based) across the United States, as well as NIH staff, and independent peer reviewers. Additionally, respondent Hoechst Marion Roussel's medical expert, Dr. Norman Kaplan, relies upon and cites to the JNC 6 Report in his expert report submitted in this matter.

The OTA Study was prepared at the request of the United States Congress House Committee on Energy and Commerce and its Subcommittee on Health and the Environment, and it was endorsed by the Senate Committee on the Judiciary's Subcommittee on Antitrust, Monopolies, and Business Rights. The Office of Technology Assessment was assisted in preparing the study by an advisory panel of business, consumer, and academic leaders. The study presents an in-depth examination of the costs of pharmaceutical research and development ("R&D"), the economic rewards from that investment, and the impact of public policies on both the costs and returns of pharmaceutical R&D.

Finally, the Food and Drug Administration has proposed amendments to its regulations governing 180-day generic drug exclusivity under the Federal Food, Drug, and Cosmetic Act, which is found at 64 Fed. Reg. 42,873 (1999), to clarify existing eligibility requirements for abbreviated new drug application (ANDA) sponsors. The proposed amendments include a discussion of the background and rationale for changing the current regulations governing 180-day generic drug exclusivity.

The facts that we ask Your Honor to take official notice of are not about the parties to this litigation (that is, they are not "adjudicative facts"), but concern broader facts touching upon policy and law that cannot seriously be contested in the adjudication of this matter. Further, we believe that taking official notice of these fact will assist Your Honor, in the first instance, and

the Commission and possibly the court of appeals, in deciding issues relevant to the ultimate resolution of this matter. Accordingly, we respectfully request that Your Honor take official notice of the following facts:[8]

1. In 1996, 43 percent of the prescription drugs sold in the United States (as measured in total countable units, such as tablets and capsules) were generic. CBO Study at p. ix.

2. Generic drugs contain the same active ingredient as a brand-name drug (CBO Study at p. 1) and are judged by the Food and Drug Administration to be comparable in terms of such factors as strength, quality, and therapeutic effectiveness. CBO Study at p. 2.

3. Generic drugs cost less than their brand-name, or "innovator," counterparts. Thus, they have played an important role in holding down national spending on prescription drugs from what it would otherwise have been. Considering only sales through pharmacies, the Congressional Budget Office estimates that by substituting generic for brand-name drugs, purchasers saved roughly $8 billion to $10 billion in 1994 (at retail prices). CBO Study at p. ix.

4. Three factors are behind the dramatic rise in sales of generic drugs. First, the Drug Price Competition and Patent Term Restoration Act of 1984 -- commonly known as the Hatch-Waxman Act -- made it easier and less costly for manufacturers to enter the market for generic drugs. Second, by 1980, most states had passed drug-product substitution laws that allowed pharmacists to dispense a generic drug even when the prescription called for a brand-name drug. Third, some government health programs, such as Medicaid, and many private health insurance plans have actively promoted such generic substitution. CBO Study at p. ix.

5. The Hatch-Waxman Act tried to balance two competing objectives: encouraging competition from generic drugs while maintaining the incentives to invest in developing innovative drugs. CBO Study at p. ix.

6. The Hatch-Waxman Act eliminated the duplicative tests that had been required for a generic drug to obtain approval from the Food and Drug Administration. Before 1984, manufacturers of generic drugs were required to independently

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[8] The text of the facts set forth below for the most part is taken verbatim from the respective studies, reports, and regulations that are cited. Some editing has been made to improve readability and to facilitate comprehension, including the omission of footnotes.

prove the safety and efficacy of their products, and they were prohibited from using unpublished test results of the original innovator drug, which were considered trade secrets of its manufacturer. CBO Study at p. xii.

7. The Hatch-Waxman Act streamlined the process for approving generic drugs by requiring only that manufacturers demonstrate "bioequivalence" to an already-approved innovator drug. (Bioequivalence means that the active ingredient is absorbed at the same rate and to the same extent for the generic drug as for the innovator drug.) The tests necessary to prove bioequivalence are much less costly than those required to prove safety and efficacy. CBO Study at p. xii.

8. By accelerating the approval process for a generic drug and also allowing its producer to begin clinical tests before the patent on the innovator drug has expired, the Hatch-Waxman Act has reduced the average delay between patent expiration and generic entry from more than three years to less than three months for top-selling drugs. Even more important, the act increases the proportion of brand-name drugs that face generic competition once their patents expire. CBO Study at p. xii.

9. After an innovator drug's patent expires, generic copies quickly gain a large share of its market. The Congressional Budget Office examined 21 brand-name prescription drugs in its retail pharmacy data set that first saw generic competition between 1991 and 1993. Within their first full calendar year after patent expiration, those drugs lost an average of 44 percent of their market (as measured by the quantity of prescription drugs sold through pharmacies) to generic drugs. And the generic versions cost an average of 25 percent less than the original brand-name drugs at retail prices. CBO Study at p. xiii.

10. By making generic entry easier and less costly, the Hatch-Waxman Act helped increase the number of generic manufacturers producing the same drug. As the number of manufacturers rises, the average prescription price of a generic drug falls. The Congressional Budget Office's analysis shows that when one to ten firms are manufacturing and distributing generic forms of a particular drug, the generic retail price of that drug averages about 60 percent of the brand-name price. When more than 10 manufacturers have entered the market, the average generic prescription price falls to less than half of the brand-name price. CBO Study at p. xiii.

11. Manufacturers of brand-name drugs invest an average of about $200 million (in 1990 dollars) to bring a new drug to market, when the cost of capital and the cost of failures (that is, investments in drugs that never make it to the market) are included. CBO Study at p. xiii.

12. Discovering and developing a drug takes 11 to 12 years. CBO Study at p. 14.

13. The dramatic rise in generic sales since 1984 has held down average prices for drugs that are no longer protected by a patent. Those lower prices, however, tend not to result from reductions in price of the original brand-name drugs when it begins facing competition from generic drugs. Rather, average prices fall primarily because consumers switch from the higher-priced innovator drug to the lower-priced generics. CBO Study at p. 13.

14. Since generic prices tend to fall as the number of producers rises, generic manufacturers are most profitable when they are one of the first to enter a market. CBO Study at p. 32.

15. Manufacturers of generic drugs, who sell nearly identical versions of the same product, compete more intensely on the basis of price than do manufacturers of innovator drugs, who compete more on the basis of quality and other differences between products. CBO Study at p. 35.

16. A schematic diagram of the payment system for prescription drugs, including how pharmaceutical benefit management companies ("PBMs") fit into this payment system, is set forth in the CBO Study, figure 1, at page 8. (Attached to this motion at Tab 1).

17. A schematic diagram of the distribution channels for prescription drugs is set forth in the CBO Study, figure 2, at page 14. (Attached to this motion at Tab 2).

18. A table showing the changes in patent protection for U.S. pharmaceuticals, comparing times before and after the enactment of the Hatch-Waxman Act, is set forth in the CBO Study, table 7, at page 39. (Attached to this motion at Tab 3).

19. The Food and Drug Administration's median total time for approval of new drugs acted on in 1998 was 12 months. Approval time represents the total review time at the FDA plus the time for the innovator drug companies' response to the FDA's requests for additional information. CDER Report at p. 6.

20. The Food and Drug Administration's median approval time for generic drugs in 1998 was 18 months. CDER Report at p. 14.

21. A schematic diagram of the development process for new drugs, including the average amount of time it takes to complete each phase of new drug development, is set forth in the CDER Fact Book at page 16. (Attached to this motion at Tab 4).

22. The steps necessary to complete the generic drug review process, including a schematic diagram of that process and a description of each step, is set forth in the CDER Handbook at pages 29-34. (Attached to this motion at Tab 5).

23. Heart disease and stroke remain the first and third leading causes of death, respectively, in the United States and impose an enormous financial and social burden on Americans -- more than $259 billion in direct and indirect costs a year. JNC 6 Report at p. 7.

24. Approximately 50 million adult Americans have hypertension. JNC 6 Report at p. 8.

25. Most persons with hypertension have additional risk factors for cardiovascular disease. JNC 6 Report at p. 8.

26. Hypertension is defined as systolic blood pressure (SBP) of 140 mm Hg or greater, diastolic blood pressure (DBP) of 90 mm Hg or greater, or taking antihypertensive medication. JNC 6 Report at p. 11.

27. The objective of identifying and treating high blood pressure is to reduce the risk of cardiovascular disease and associated morbidity and mortality. JNC 6 Report at p. 11.

28. The optimal formulation for antihypertensive drugs should provide 24-hour efficacy with a once-daily dose, with at least 50 percent of the peak effect remaining at the end of the 24 hours. Long-acting formulations that provide 24-hour efficacy are preferred over short-acting agents for many reasons: (a) adherence is better with once-daily dosing; (b) for some agents, fewer tablets incur lower cost; (c) control of hypertension is persistent and smooth rather than intermittent; and (d) protection is provided against whatever risk for sudden death, heart attack, and stroke that is due to the abrupt increase in blood pressure after arising from overnight sleep. JNC 6 Report at p. 23.

29. The cost of therapy may be a barrier to controlling high blood pressure and should be an important consideration by physicians in selecting antihypertensive medication for their patients. JNC 6 Report at p. 34.

30. Generic formulations are acceptable for use by physicians in treating high blood pressure. JNC 6 Report at p. 34.

31. Diltiazem hydrochloride exhibits the following side effects: nausea, headache, conduction defects, worsening of systolic dysfunction, and gingival hyperplasia. JNC 6 Report at p. 27.

32. Verapamil hydrochloride exhibits the following side effects: constipation, conduction defects, worsening of systolic dysfunction, and gingival hyperplasia. JNC 6 Report at p. 27.

33. Dihydropyridines exhibit the following side effects: edema of the ankle, flushing, headache, and gingival hypertrophy. JNC 6 Report at p. 27.

34. For patients who suffer hypertension and myocardial infarction, diltiazem and verapamil may have favorable effects compared to other medications. JNC 6 Report at p. 30.

35. Pharmaceutical research and development is a costly and risky business, but in recent years the financial rewards from R&D have more than offset its costs and risks. OTA Study at p.1.

36. Pharmaceutical R&D is an investment. The principal characteristic of an investment is that money is spent today in the hope that even more money will be returned to the investors sometime in the future. If investors (or the corporate R&D managers who act on their behalf) believe that the potential profits from R&D are worth the investment's cost and risks, then they will invest in it. Otherwise, they will not. OTA Study at p. 3.

37. The long-run persistence in the pharmaceutical industry of dollar returns higher than the amount needed to justify the cost and risk of R&D is evidence of unnecessary pricing power for pharmaceuticals. OTA Study at p. 3.

38. Despite the fact that many pharmaceutical compounds, though protected from generic competition by patents or other market exclusivity provisions, compete for market share with similar compounds, that competition tends to focus on product characteristics, such as ease of use, favorable side-effects profiles, or therapeutic effects, and not on price. Pharmaceutical companies spend a great deal on this product competition. OTA Study at p. 27.

39. Emphasizing product competition over price competition is a rational strategy for pharmaceutical companies operating in a market that is not very sensitive to price differentials among similar compounds. If prescribing physicians will not be swayed by lower prices, it would be foolhardy for firms to set prices for their products much lower than those of competitors. OTA Study at p. 27.

40. Pharmaceuticals are sold through multiple distribution channels, and pharmaceutical companies can set different prices to different kinds of buyers. For example, companies can sell direct to health maintenance organizations or large hospital chains and offer lower prices than they charge for drugs sold to

community pharmacies. The ability to charge different prices to different kinds of buyers is referred to as price discrimination. Price discrimination increases profits by separating buyers who are price sensitive from those who are not. OTA Study at pp. 27-28.

41. Health maintenance organizations, particularly those with tight organizational structures, have both the incentive and the ability to influence physicians' prescribing practices to take account of cost as well as quality. They can do this by establishing restrictive "formularies," that is, lists of drugs that can be prescribed by participating physicians without special appeals or approvals. The power to impose limitations on prescribing has given HMOs purchasing clout with manufacturers and has led manufacturers to offer substantial price discounts to some of these organizations. When there are several close substitutes in a therapeutic class, the HMO can use the formulary as a bargaining chip to exact price concessions from producers. OTA Study at pp. 28-29.

42. Hospitals also have an incentive to establish formularies for drugs administered to inpatients. In 1983, Medicare adopted a new "prospective payment system" that pays hospitals on the basis of the admission, not the specific services each patient uses. This system created incentives for hospitals to reduce both the length of stay and the cost of services offered per stay, including drugs. The incentive to develop restrictive formularies is limited, however, because most insured nonelderly hospitalized people pay for hospital care on the basis of charges for individual products and services. OTA Study at p. 29.

43. Generic drug manufacturers compete largely on the basis of price, since they can claim no quality advantage over the brand-name drug. OTA Study at p. 30.

44. Private and public health insurers have initiated programs to encourage the dispensing of cheaper versions of multisource compounds (those with generic equivalents on the market). These strategies include using mail-order pharmacies, waiving beneficiaries' cost-sharing requirements when prescriptions are filled with generic versions, or refusing to pay more than a certain amount for a drug with a generic competitor. Medicaid, the government health insurance program for the indigent, mandates substitution with cheaper generic drugs unless the prescribing physician specifically prohibits it in writing on the prescription form. These programs have substantially reduced brand-name compounds' unit sales and revenues. OTA Study at p. 30.

45. When research and development take place under conditions of rivalry, as in the pharmaceutical industry, that rivalry can lead to wasteful and duplicative R&D efforts and lower returns to the public as a whole than to private industry. That is,

the public can end up paying too much for the benefits it receives from the competitive R&D. OTA Study at p. 32.

46. Because the "appropriate" level of demand for prescription drugs in the United States cannot be inferred from the existing level of demand, it is impossible to know whether on the whole there is too much R&D or too little R&D on new drugs. OTA Study at p. 32.

47. The Hatch-Waxman Act benefits consumers by bringing lower priced generic versions of previously approved drugs to market, while simultaneously promoting new drug innovation through the restoration of patent life lost during the Food and Drug Administration's regulatory review. The award of a 180-day period of market exclusivity for applicants filing certain Abbreviated New Drug Applications ("ANDA") with so-called paragraph IV certifications was designed to maintain this balance by rewarding generic firms for their willingness to challenge uneforceable and invalid innovator patents, or design noninfringing drug products. Recently, however, this balance has been upset and generic competition impeded, in part through the establishment of certain licensing agreements or other commercial arrangements between generic and innovator companies. FDA Proposed Rule at 42,882.

48. Under current FDA regulatory provisions, the first generic applicant to file a substantially complete ANDA with a paragraph IV certification can delay generic competition by entering into certain commercial arrangements with an innovator company. The result may be that, notwithstanding the intent of the Hatch-Waxman Act, rewards are directed to generic companies for hindering rather than speeding generic competition. A necessary condition for such arrangements is that the economic gains to the innovator from delaying generic competition exceed the potential economic gains to the generic applicant from 180 days of marketing exclusivity. Such instances are becoming more frequent because a successful strategy to extend market exclusivity can mean tens of millions of dollars in increased revenue for an innovator firm. Under such circumstances, it can be mutually beneficial for the innovator and the generic company that is awarded 180 days of generic exlusivity to enter into agreements that block generic competition for extended periods. This delayed competition harms consumers by slowing the introduction of lower priced products into the market and thwarts the intent of the Hatch-Waxman Act. FDA Proposed Rule at 42,882-83.

* * * * *

For the reasons discussed above, we respectfully request that Your Honor take official notice of the facts set forth above, as well as the figures, tables, and diagrams attached to this motion.

Respectfully Submitted,

Markus H. Meier
Robin L. Moore

Counsel Supporting the Complaint

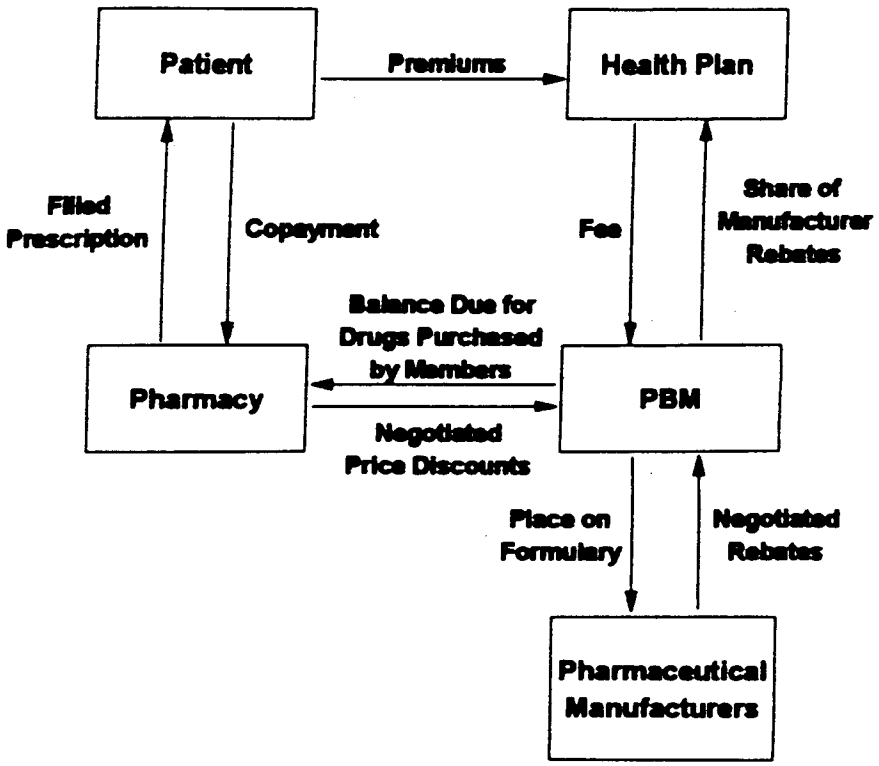
Bureau of Competition
Federal Trade Commission
Washington, D.C. 20580

Dated: November 15, 2000

Tab 1

The Payment System for Prescription Drugs
(CBO Report, Figure 1, p. 8)

Figure 1.
How PBMs Fit Into the Payment System for Prescription Drugs



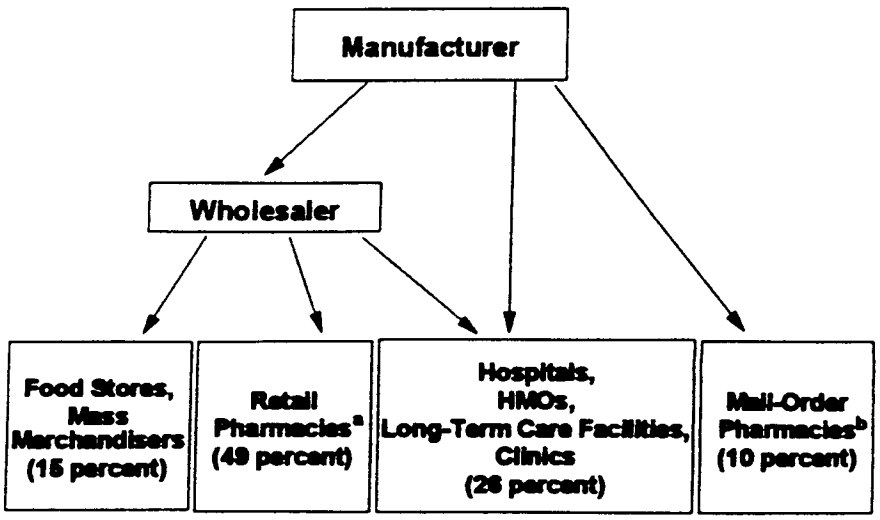
SOURCE: Congressional Budget Office based in part on General Accounting Office, *Pharmacy Benefit Managers: Early Results on Ventures with Drug Manufacturers*, GAO/HEHS-96-45 (November 1995).

NOTE: PBMs = pharmaceutical benefit management companies.

Tab 2

Channels of Distribution for Prescription Drugs
(CBO Report, Figure 2, p.14)

Figure 2.
Channels of Distribution for Prescription Drugs



SOURCE: Congressional Budget Office based on Micky Smith, *Pharmaceutical Marketing Strategy and Cases* (New York: Pharmaceutical Products Press, 1991), Chapter 3; Boston Consulting Group, *The Changing Environment for U.S. Pharmaceuticals* (Boston: Boston Consulting Group, April 1993); and Pharmaceutical Research and Manufacturers of America, *1997 Industry Profile* (Washington, D.C.: PhRMA, March 1997), p. 31.

NOTES: Figures in parentheses represent shares of the prescription drug market in 1996, calculated as a percentage of total U.S. sales at manufacturer prices.

HMOs = health maintenance organizations.

a. Some chain-store pharmacies buy directly from the manufacturer.

b. Some mail-order pharmacies go through a wholesaler.

Tab 3

Changes in Patent Protection for U.S. Pharmaceuticals

(CBO Report, Table 7, p. 39)

Table 7.
Changes in Patent Protection for U.S. Pharmaceuticals

	Before the Hatch-Waxman Act of 1984	After the Hatch-Waxman Act and the Uruguay Round Agreements Act of 1994
Patent Term	17 years from patent grant	20 years from application filing (the earliest relevant filing date)[a]
Average Period of Marketing Under Patent Protection[b]	About 9 years	About 11.5 years
Usual Period Between Patent Expiration and Generic Entry[c]	3 to 4 years	Frequently 1 to 3 months
Average Generic Market Share for Multiple-Source Drugs (Percent)[d]	12.7	57.6

SOURCE: Congressional Budget Office based in part on the sources in the footnotes below.

NOTE: These figures exclude antibiotics, which were not affected by the Hatch-Waxman Act.

a. See 35 U.S.C. 154(c)(1). For drugs patented before June 8, 1995, companies can choose between the 17-years-from-patent term and the 20-years-from-filing term (if the drug was not yet into its Hatch-Waxman extension on that date).

b. The average "effective" patent term (the period between approval by the Food and Drug Administration and patent expiration). These averages differ from the sales-weighted averages used in calculating the returns from marketing a new drug. Top-selling drugs tend to have more years of marketing under patent protection, making the sales-weighted averages larger. The figure for the pre-Hatch-Waxman period is based on Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards* (February 1993); and Henry Grabowski and John Vernon, "Longer Patents for Lower Imitation Barriers: The 1984 Drug Act," *American Economic Review*, vol. 76, no. 2 (May 1986). The figure for the post-Hatch-Waxman period is based on the average effective patent term for the 51 drugs approved between 1992 and 1995 that received a Hatch-Waxman extension.

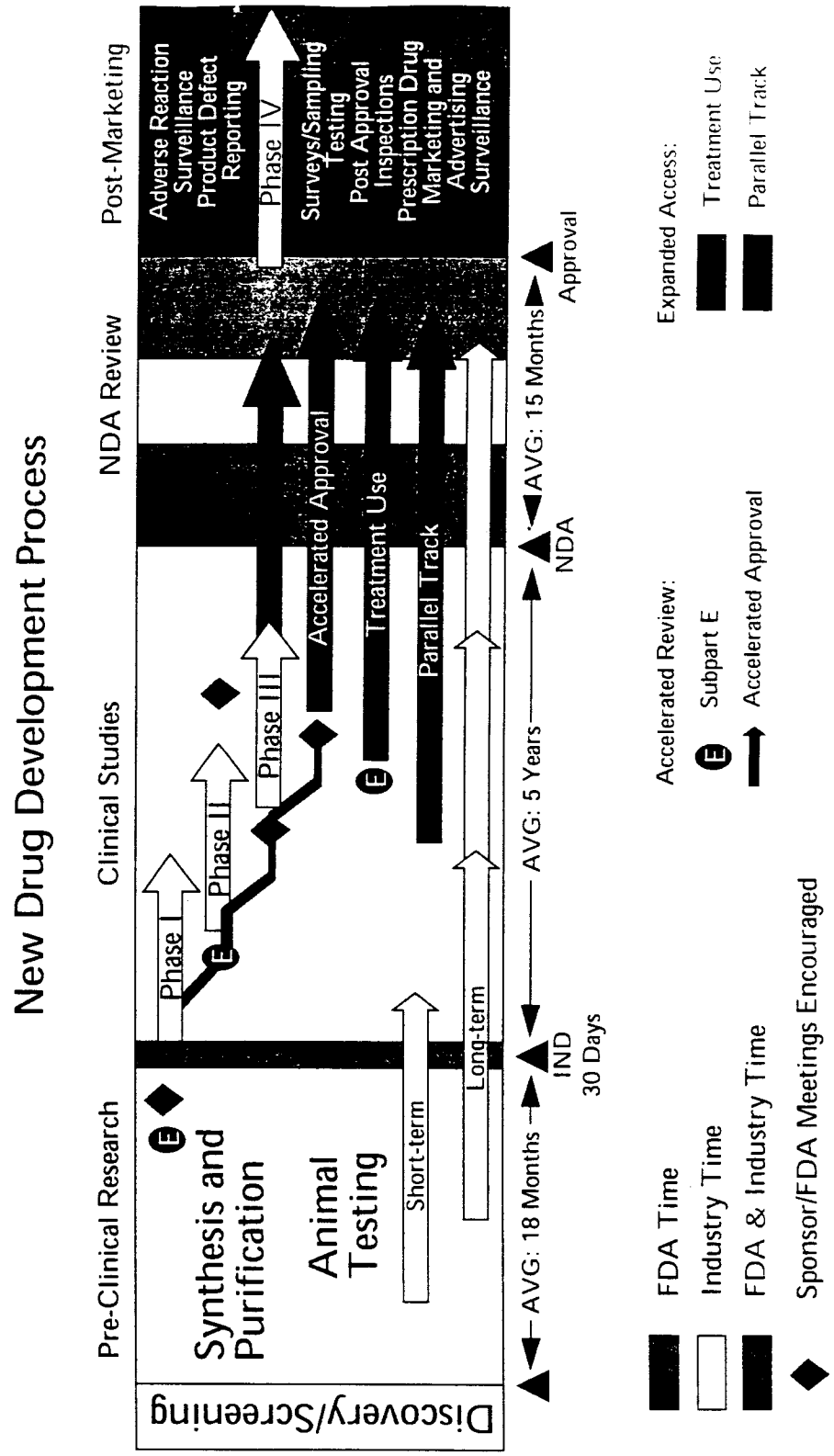
c. The pre-Hatch-Waxman figure is based on CBO's analysis of generic entry for 11 nonantibiotic drugs approved after 1962. The post-Hatch-Waxman figure is based in part on Henry Grabowski and John Vernon, "Longer Patents for Increased Generic Competition in the U.S.: The Hatch-Waxman Act After One Decade," *PharmacoEconomics* (1996).

d. The increase resulted from various changes in the structure of demand for brand-name and generic drugs as well as from changes in the Hatch-Waxman Act. The pre-Hatch-Waxman figure is based on sales data for 29 multiple-source drugs (excluding antibiotics) in Table A5-1 of Alison Masson and Robert Steiner, *Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws* (Federal Trade Commission, October 1985).

Tab 4

New Drug Development Process

(CDER Fact Book, p. 16)



Tab 5

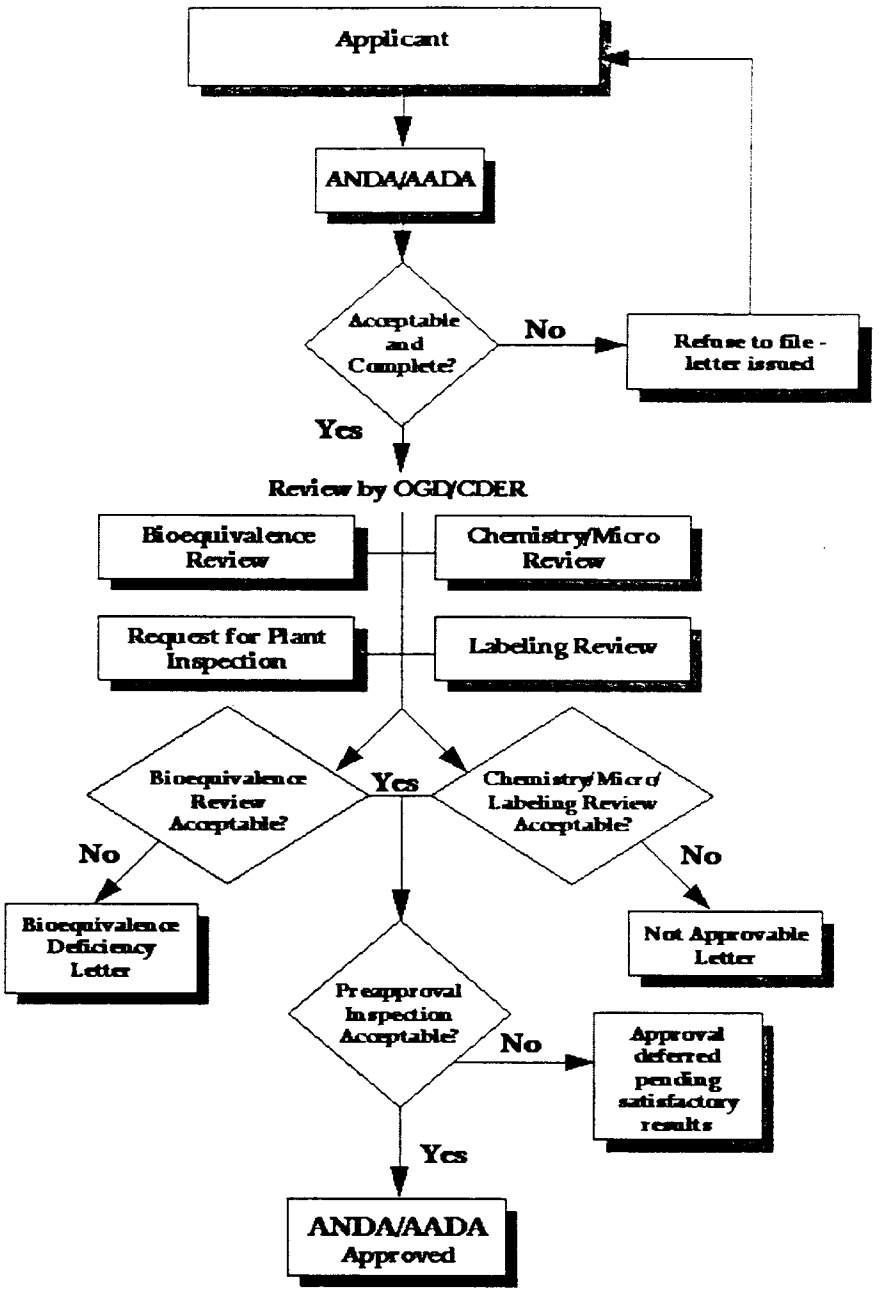
Generic Drug Review Process

An important part of CDER's mission is to assure that safe and effective generic drugs are available to the American people. This work is accomplished in CDER's Office of Generic Drugs (OGD). The information below provides an understanding of how CDER works to assure the safety and effectiveness of generic drug products.

- Generic Drug Review Process- An interactive chart that provides an overview of CDER's abbreviated new drug application (ANDA) and abbreviated antibiotic drug application (AADA) review process, and how CDER determines the safety and bioequivalence of generic drug products prior to approval for marketing..... 30

- OGD Home Page- For further information on CDER's generic drug program, visit the Office of Generic Drugs home page at http://www.fda.gov/cder/ogd/index.htm.

Generic Drug (ANDA/AADA) Review Process



Applicant

An applicant is any person (usually a firm) who submits an abbreviated new drug application (ANDA) or an abbreviated antibiotic drug application (AADA) to obtain FDA approval to market a generic drug product and any person who owns an approved application or abbreviated application.

Abbreviated new drug applications under 21 CFR subpart 314.94, and amendments, supplements, and resubmissions; and Abbreviated antibiotic drug application submissions, as well as items sent by parcel post or overnight courier service to the Office of Generic Drugs, should be directed to:

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ANDA/AADA

A generic drug product is one that is comparable to an innovator drug product (also known as the reference listed drug (RLD) product as identified in the FDA's ***list of Approved Drug Products with Therapeutic Equivalence Evaluations***) in dosage form, strength, route of administration, quality, performance characteristics and intended use.

Abbreviated new drug applications (ANDA's) and abbreviated antibiotic drug applications (AADA's) are submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs for review and approval. Once approved an applicant may manufacture and market the generic drug product provided all patent protection and exclusivity associated with the RLD have expired.

Generic drug applications are termed "abbreviated" in that they are not required to provide clinical data to establish safety and efficacy, since these parameters have already been established by the approval of the innovator drug product (first approved version of the drug product marketed under a brand name).

Subject-Related CDER Guidances of Interest

- Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application

- Submitting Application Archival Copies in Electronic Format (DRAFT ONLY)

- Drug Master Files

Acceptable and Complete?

An application must contain sufficient information to allow a review to be conducted in an efficient and timely manner. An initial assessment of completeness and acceptability is performed by the project manager. This initial review documents that the application contains all the necessary components and is, therefore, acceptable for filing and review.

Refuse to File Letter Issued

If the application is missing one or more essential components, a Refuse to File letter is issued to the applicant. The letter identifies the missing component(s) and informs the applicant that the application will not be filed until it is complete.

Bioequivalence Review

FDA requires an applicant to provide information to establish bioequivalency. Such information may include:

- a formulation comparison for products whose bioavailability is self evident, for example, oral solutions, injectables, or ophthalmic solutions where the formulations are identical;
- comparative dissolution testing where there is a known correlation between in vitro and in vivo effects;
- in vivo bioequivalence testing comparing the rate and extent of absorption of the generic to the reference product; and
- for non-classically absorbed products, a head-to-head evaluation of comparative effectiveness based upon clinical endpoints.

Chemistry/Microbiology Review

The Chemistry/Microbiology review provides assurance that the generic drug will be manufactured in a controlled consistent manner. Areas such as manufacturing procedures, raw material specifications and controls, sterilization processes and validation, container and closure systems, and stability are reviewed to assure that the drug will perform in an acceptable manner.

Request for Plant Inspection

Upon filing an ANDA/AADA an establishment evaluation request is forwarded to CDER's Office of Compliance to determine whether the product manufacturer, the bulk drug substance manufacturer, and any outside testing or packaging facilities are operating in compliance with current Good Manufacturing Practice regulations as outlined in *21 CFR 211*. Furthermore, a preapproval product specific inspection may be performed on certain applications to assure data integrity.

Labeling Review

The labeling review ensures that the proposed generic drug labeling is identical to that of the reference listed drug except for differences due to a change in manufacturer, patent or exclusivity issues, or if approval is based upon a suitability petition. Furthermore, the labeling review serves to identify and resolve issues of confused or mistaken identity that may arise in drug labeling in an effort to avoid drug mix-ups and prevent medication errors.

Bioequivalence Review Acceptable?

If the Bioequivalence Review determines that there are deficiencies in the Bioequivalence portion of the application, then a Bioequivalence deficiency letter is issued to the applicant. The deficiency letter will detail the deficiencies and request information and data to resolve the deficiencies. If the review determines the bioequivalence portion of the application is acceptable, a letter indicating that there are no further questions at that time will be issued.

Chemistry/Micro/Labeling Review Acceptable?

If there are deficiencies involved in the Chemistry/Manufacturing/Controls, Microbiology or Labeling portions of the application, these deficiencies are communicated to the applicant in a not approvable letter. The letter instructs the applicant to provide information and data to address the deficiencies and provides regulatory direction on how to amend their application. If the above sections are found to be acceptable, as well as the preapproval inspection and bioequivalence portion of the application, then the application moves to approval and an approval or tentative approval letter is issued.

Preapproval Inspection Acceptable?

A satisfactory recommendation from the Office of Compliance based upon an acceptable preapproval inspection is required prior to approval. If an unsatisfactory recommendation is received, a not approvable letter may be issued. In such a case, approval of the generic drug product will be deferred pending a satisfactory re-inspection and recommendation.

ANDA/AADA Approved

After all components of the application are found to be acceptable, an approval or tentative letter is issued to the applicant detailing the conditions of the approval and providing them with the ability to market the generic drug product. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the tentative approval of the generic drug product until the patent/exclusivity condition has expired. A tentative approval does not allow the applicant to market the generic drug product.

CERTIFICATE OF SERVICE

I, Markus H. Meier, hereby certify that on November 15, 2000, I caused a copy of the Complaint Counsel's Motion for Official Notice to be served upon the following persons via overnight delivery.

Michael L. Koon, Esq.
Shook, Hardy & Bacon, L.L.P
600 14th Street, N.W.
Suite 800
Washington, DC 20005-2004

Peter O. Safir, Esq.
Kleinfeld, Kaplan, and Becker
1140 19th Street, N.W.
9th Floor
Washington, DC 20036

Louis M. Solomon
Solomon, Zauderer, Ellenhorn,
Frischer, & Sharp
45 Rockefeller Plaza
New York, NY 10111

Markus H. Meier
Counsel Supporting the Complaint