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# RECENT CHANGES IN U.S. FOOD AND DRUG LAW:

# IMPLICATIONS FOR DRUG DEVELOPMENT

by

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## Abstract

This paper examines in detail the Waxman/Hatch Act and the NDA Rewrite, from both an implementation point of view and from a world-wide research and development perspective. The central theme of these regulatory changes appears to be consistent with U.S. drug policy of the past two decades, i.e.,cost containment, primarily, follwed by uniformity and efficiency in the regulatory review process. These recent changes, just as the 1962 Drug Ammendments 22 years earlier, will continue to have profound effects upon the sites at which pharmaceutical research and development is carried out.

## Introduction

### Background

Changes in U.S. Food and Drug Law during the last 25 years may be viewed as a pendulum whose swing had become extreme. Beginning with the 1962 drug announcements, when all drug development was placed under the supervision of the F.D.A., U.S. regulations have created a somewhat hostile environment, from an administrative and economic point of view, in which to develop drugs. Moreover, other industrialized nations such as Japan and France, have at the same time, significantly improved their environments for drug discovery and development. An examination of the history of U.S. Drug Regulation and its impact, will place in perspective the more recent changes and their likely implications for future drug development.

#### U.S. Food and Drug Law: An Historical Perspective

It is clear that the number of compounds receiving Food and Drug Administration approval has dwindled since the 1962 Drug Ammendments. The number of drugs representing major therapeutic gains (by Food and Drug Administration standards) has also been few, as demonstrated in Table III. An assessment of the United States' situation as reflected in the following tables, was offered by Dr. Francoise Florent, Director of Clinical Research Laboratoires Joullie, France, at the IFPMA International Drug Registration Symposium in 1979, as follows:

TABLE I

NEW THERAPEUTIC SUBSTANCES DISCOVERED BETWEEN 1961-1973 BY COUNTRY OF ORIGIN

| WHERE INVENTED | PERCENTAGE |
|---|---|
| United States | 23.9 |
| France | 20.9 |
| Federal Republic of Germany | 12.9 |
| Japan | 9.6 |
| Switzerland | 7.8 |
| Italy | 6.5 |
| Great Britain | 4.9 |
| Socialist Countries | 4.5 |
| Scandinavia | 3.3 |
| Benelux Countries | 2.9 |
| Austria | 1.5 |
| Others | 1.3 |

SOURCE: D. Poggiolini, "The Acceptance of International Clinical Data," Symposium on International Drug Registration (Geneva, Switzerland: International Federation of Pharmaceutical Manufacturers Association, October 2-5, 1979), p. 99.

"(The data) demonstrated . . . to what extent excessive severity of regulation can prevent innovation from reaching those to benefit from it, that is the patient. This is well demonstrated in the United States."

A study by Wardell compared new drugs introduced in the United States following the 1962 Amendments with those in the

TABLE II

NEW THERAPEUTIC SUBSTANCES INTRODUCED BETWEEN 1961-1973 BY COUNTRY IN WHICH INITIAL MARKETING TOOK PLACE

| FIRST INTRODUCED IN | PERCENTAGE |
|---|---|
| France | 23.6 |
| Federal Republic of Germany | 15.1 |
| Japan | 10.0 |
| Great Britain | 9.8 |
| United States | 9.0 |
| Italy | 6.6 |
| Switzerland | 5.3 |
| Socialist Countries | 4.4 |
| Benelux Countries | 4.0 |
| Scandinavia | 2.3 |
| Austria | 1.5 |
| Others | 8.4 |

SOURCE: D. Poggiolini, "The Acceptance of International Clinical Data," Symposium on International Drug Registration (Geneva, Switzerland: International Federation of Pharmaceutical Manufacturers Association, October 2-5, 1979), p. 100.

United Kingdom. For the ten year period, 1962 1972, fifty percent more compounds were registered and marketed in the United Kingdom than in the United States. (1:773-790)

A basic effect of the IND regulations has been to shift the sites of preclinical and early clinical research from the United States to Europe and Japan. This has been caused by the

TABLE III

NEW DRUGS APPROVED FOR MARKETING IN THE USA
FROM OCTOBER 1975 - MARCH 1979

| THERAPEUTIC GAIN | NUMBER |
|---|---|
| Major | 11 |
| Moderate | 32 |
| Minor to None | 185 |
| TOTAL | 228 |

SOURCE: D. Poggiolini, "The Acceptance of International Clinical Data," Symposium on International Drug Registration (Geneva, Switzerland: International Federation of Pharmaceutical Manufacturers Association, October 2-5, 1979), p. 94.

timing and flexibility difficulties for multinational drug development posed by these regulations.

The IND regulations generally fail to recognize that drug development is a pioneering process. As a new chemical entity is developed, there is a learning experience throughout every stage in the process which affects all subsequent stages.

It is impractical to plan drug development and carry out research according to the requirements of the IND regulations. The situation is even more pronounced when viewed within the scope of multinational development activities.

If we examine the IND requirements which pose particular problems for drug development, the following are critical:

A. Statement of the composition of the formulation with alternate inactive ingredients specified. Prior to clinical testing the specification of a final dosage form and its composition is impractical. At the IND stage, assays for the active ingredient may still be in development. Formulation work will normally not be completed until the human pharmacokinetics (Phase I) and primary clinical indication are established (late Phase II). Therefore, the IND requirements for stating the final formulation are extremely difficult to comply with. Multinational firms, in an effort to deal with this (and the other) IND requirements have turned to other countries for early clinical testing in order to get important clinical studies run without committing themselves to a final formulation.

B. Statement of source(s) of each new drug used as a raw material or starting material. Sourcing of formulation materials is a changing process which runs parallel to changes in the formulation itself, based on knowledge gained in clinical studies (as explained below), and efforts to decrease the cost of goods. For these processes to proceed, it is necessary from and industry point of view to develop clinical data in a country where sourcing of formulation materials may be quickly changed without regulatory delays. This oversight in the IND regulations added momentum to early stage foreign

drug development. Only after sourcing is finalized is it practical to submit the United States' IND.

C. Provision of clinical study plan by phases. Prior to clinical study, it is difficult and rather impractical to formulate a complete study plan for any drug. With only animal data in hand, pharmacokinetics, safety and efficacy (primary and secondary indications) cannot be accurately forecast. This requirement is unique to the United Stdtes. It has caused not only a great deal of delay in American drug development, but has given a great inducement to the industry to begin clinical development in foreign countries. Following clinical study abroad, a reasonable clinical trial plan can be formulated for the United States.



## The U.S. "Drug Lag"

Many studies have been carried out in an effort to document the "drug lag" (time difference between foreign drug registration and NDA approval) and explain its causes. The available studies have basically addressed peripheral symptoms of the drug lag issue. Hansen's "Analysis of the Effects of Incremental Costs on Pharmaceutical Innovation," found that the "costs and delays associated with unneeded regulatory compliance requirements . . . reduced research productivity (in the United States) between 20% and 30% a year." (2:6)

Eisman and Wardell performed an incremental time study to determine the delays in United States' drug marketing due to

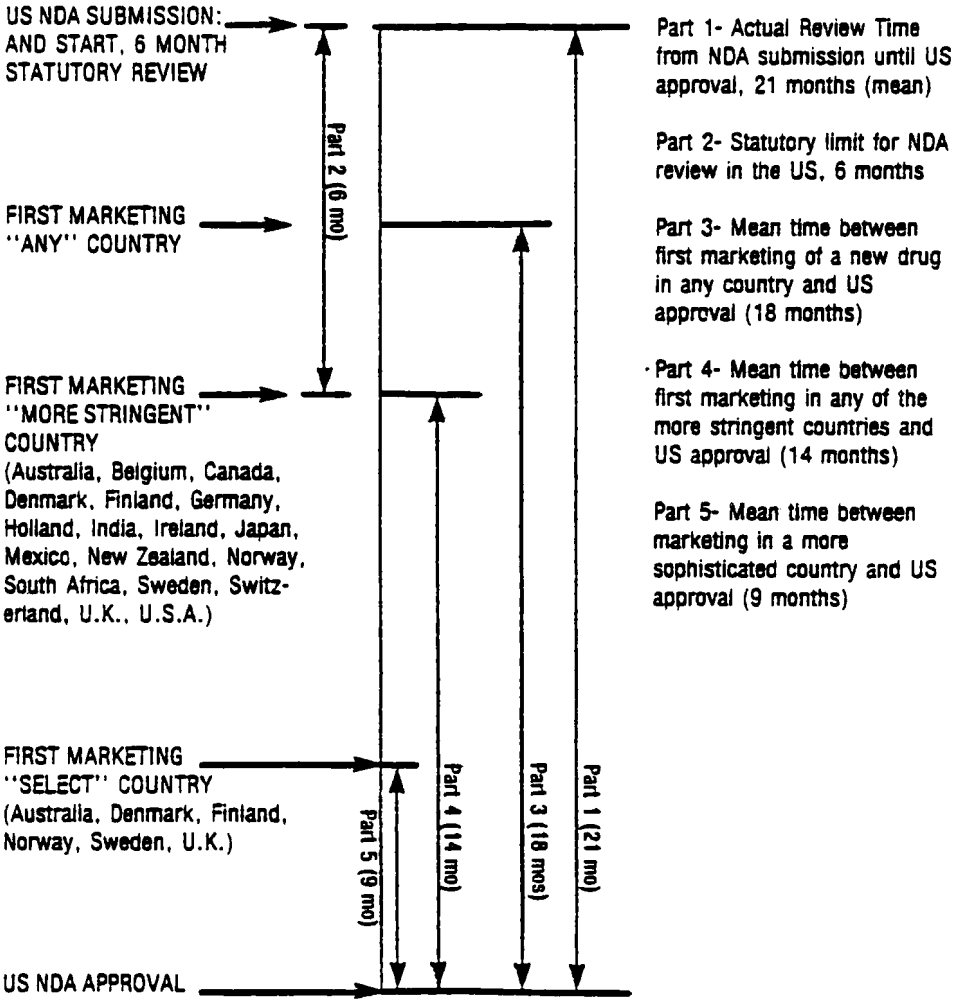
the regulatory environment. (3) These investigators compared the time to marketing introduction of drugs in the United States and other countries with similar regulatory standards. They found a drug lag of an average of fourteen months to exist between 1970 and 1979.

A table of time intervals found in the Eisman/Wardell study is presented in Figure 2 to provide a basis for drug regulatory timing as it existed in the 1970s. A key point elucidated in the Eisman/Wardell study is the fact that the staffing levels of the Food and Drug Administration New Drug Reviewers remained constant from 1971-1979, while the workload per reviewer doubled. (3:65)

Arthur Anderson and Company performed an analysis of the unnecessary costs associated with American drug regulation. (4) Nine companies reported added costs of $117 million in 1978 associated with (in the opinion of the companies) unnecessary regulatory requirements. More than 50% of the costs were associated with:

1. Clinical pharmacology trials
2. Information provided for advertising
3. Good Manufacturing Practices for injectable products
4. Antibiotic certification
5. Record keeping and reporting for NDAs
6. Labeling and package information

## EISMAN/WARDELL TIME INCREMENT STUDY




SOURCE: M. M. Eisman and W. M. Wardell, "Incremental Time Study: An Analysis of Time Spent in the Development and Approval of Drugs for the U.S. Market," Economic Costs of FDA Regulations: A Set of Studies of Some Economic Effects of Food and Drug Administration Regulation of Human Pharmaceuticals (Washington, D. C.: Pharmaceutical Manufacturers Association, March 1981), p. 62.

**FIGURE 2**

Extra paper work resulting from "unnecessary" regulations was estimated at 100,000 pages per company in 1978. The Anderson study did not address lost opportunities which resulted from American regulatory burdens.

Other studies (5 & 6) have provided similar types of information. A study carried out by the United States General Accounting Office (5) focused on the drug lag associated with new drugs classified by the Food and Drug Administration as important therapeutic advances (July 1975 -- February 1978). All but one of the fourteen drugs so classified during this period was registered and marketed abroad first. The average regulatory approval time ranged from six months in the United Kingdom to twenty-three months in the United States.

Grabowski, Vernon and Thomas performed an analysis of the effects of international drug regulations upon pharmaceutical innovation. With regard to the United States, these authors found that "regulation had more than doubled the cost of a new entity in the United States in the first decade after the new regulations (1962 Drug Amendments) were in place." (7:179)

The sum of these studies is that an increase in drug development time and costs since the 1962 Drug Amendments has occurred, with a resultant decrease in American pharmaceutical innovation.

Table IV and Figure 3 provide both support for the preceding section and introduction for the section on patents that follows.

TABLE IV

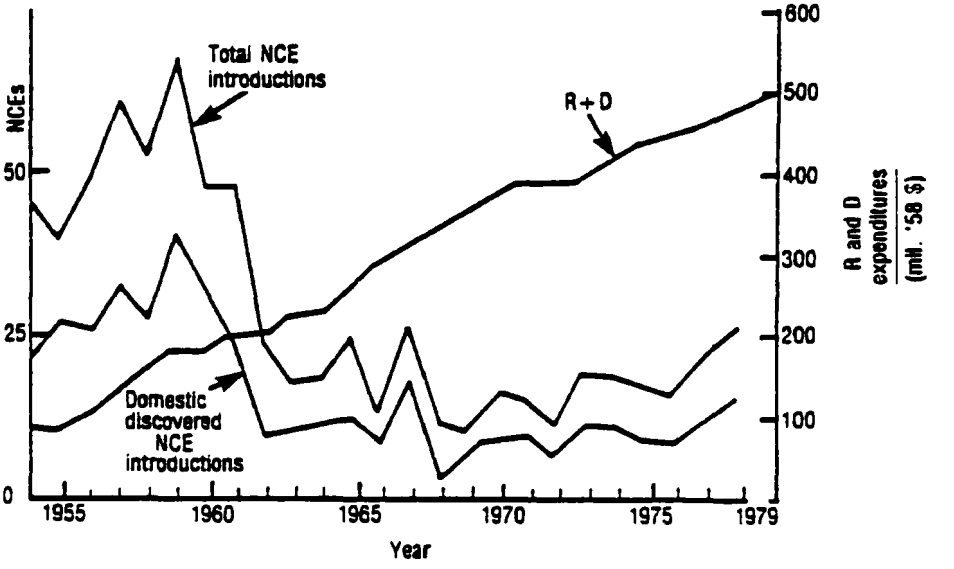
NDAs APPROVED FOR NCEs BY FIFTEEN COMPANIES

| YEAR | NUMBER OF NDAs APPROVED | MEAN NUMBER OF YEARS FOR DEVELOPMENT AND APPROVAL |
|---|---|---|
| 1963 | 0 | |
| 1964 | 0 | |
| 1965 | 0 | |
| 1966 | 3 | 2.7 |
| 1967 | 2 | 3.0 |
| 1968 | 2 | 4.0 |
| 1969 | 2 | 3.0 |
| 1970 | 5 | 5.0 |
| 1971 | 3 | 5.7 |
| 1972 | 5 | 5.2 |
| 1973 | 5 | 6.6 |

SOURCE: David Schwartzman, Innovation in the Pharmaceutical Industry (Baltimore: The Johns Hopkins University Press, 1976), p. 68.

Drug Patents - Relationship to American Pharmaceutical Research and Development

Drug patents represent perhaps the purest measure available of successful research activity. The number and quality of new drug patents provide a basis for comparing research and success over time as well as the relative success of one country vs. another.




SOURCE: H. G. Grabowski, "Public Policy and Innovation: The Case of Pharmaceuticals," Technovation, vol. 1 (1982), p. 172.

**FIGURE 3**

**DISCOVERIES AND INTRODUCTIONS OF NEW CHEMICAL ENTITIES AND TOTAL PHARMACEUTICAL RESEARCH AND DEVELOPMENT EXPENDITURES IN THE UNITED STATES 1954-1979**

Since 1972, Amercian drug patent filings have stabilized at about 2,200 per year (see Table V). Since 1974, foreign filings for American drug patents have been approximately equal to those domestically discovered (see Table V). In 1963, approximately two-thirds of all United States' patents were awarded for domestically discovered compounds.

The quality of the newly patented compounds may be indirectly assessed by examining the number of new drugs

## TABLE V

### DRUGS AND MEDICINES, NUMBER OF NEW UNITED STATES PATENTS 1963-1977

| | Number of new patents issued | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1963 | 1964 | 1965 | 1966 | 1967 | 1968 | 1969 | 1970 | 1971 | 1972 | 1973 | 1974 | 1975 | 1976 | 1977 | TOTAL |
| Total Patents | 1532 | 1802 | 1865 | 2552 | 2438 | 1664 | 2630 | 2537 | 2417 | 3843 | 3166 | 3795 | 4385 | 4720 | 4168 | 43514 |
| Originating in the United States | 1034 | 1180 | 1182 | 1703 | 1637 | 1164 | 1654 | 1596 | 1509 | 2292 | 1817 | 2059 | 2426 | 2448 | 2235 | 25936 |
| Originating in other countries* | 498 | 622 | 683 | 849 | 801 | 500 | 976 | 941 | 908 | 1551 | 1349 | 1736 | 1959 | 2272 | 1933 | 17578 |
| Patents originating in the United States | 1034 | 1180 | 1182 | 1703 | 1637 | 1164 | 1654 | 1596 | 1509 | 2292 | 1817 | 2059 | 2426 | 2448 | 2235 | 25936 |
| Owned by United States corporations | 923 | 1091 | 1082 | 1544 | 1496 | 1051 | 1520 | 1456 | 1383 | 1979 | 1631 | 1816 | 2189 | 2290 | 2053 | 23504 |
| Owned by United States individuals | 71 | 61 | 74 | 124 | 103 | 61 | 75 | 96 | 99 | 268 | 127 | 184 | 141 | 89 | 121 | 1694 |
| Owned by United States government | 25 | 22 | 23 | 21 | 21 | 17 | 23 | 19 | 22 | 32 | 51 | 42 | 67 | 41 | 43 | 469 |
| Foreign owned | 15 | 6 | 3 | 14 | 17 | 35 | 36 | 25 | 5 | 13 | 8 | 17 | 29 | 28 | 18 | 269 |
| Patents originating in other countries | 498 | 622 | 683 | 849 | 801 | 500 | 976 | 941 | 908 | 1551 | 1349 | 1736 | 1959 | 2272 | 1933 | 17578 |
| United States owned | 90 | 116 | 152 | 166 | 164 | 121 | 226 | 254 | 166 | 259 | 222 | 330 | 354 | 371 | 303 | 3294 |
| Foreign owned | 408 | 506 | 531 | 683 | 637 | 379 | 750 | 687 | 742 | 1292 | 1127 | 1406 | 1605 | 1901 | 1630 | 14284 |
| Foreign corporations | 377 | 462 | 477 | 622 | 587 | 357 | 690 | 628 | 675 | 1097 | 990 | 1251 | 1478 | 1791 | 1534 | 13016 |
| Foreign governments | | | | | 3 | 1 | 2 | 1 | 1 | | | 2 | 4 | 3 | 3 | 20 |
| Foreign individuals | 31 | 44 | 54 | 61 | 47 | 21 | 58 | 58 | 66 | 195 | 137 | 153 | 123 | 107 | 93 | 1248 |

*The Patent Office credits patents to the country of residence shown by the inventor on the patent application.

SOURCE: Pharmaceutical Manufacturers Association, Prescription Drug Industry: Pharmaceuticals, Medical Devices and Diagnostic Products - Fact Book 1980 (Washington, D.C.: Pharmaceutical Manufacturers Association, 1980), p. 41.

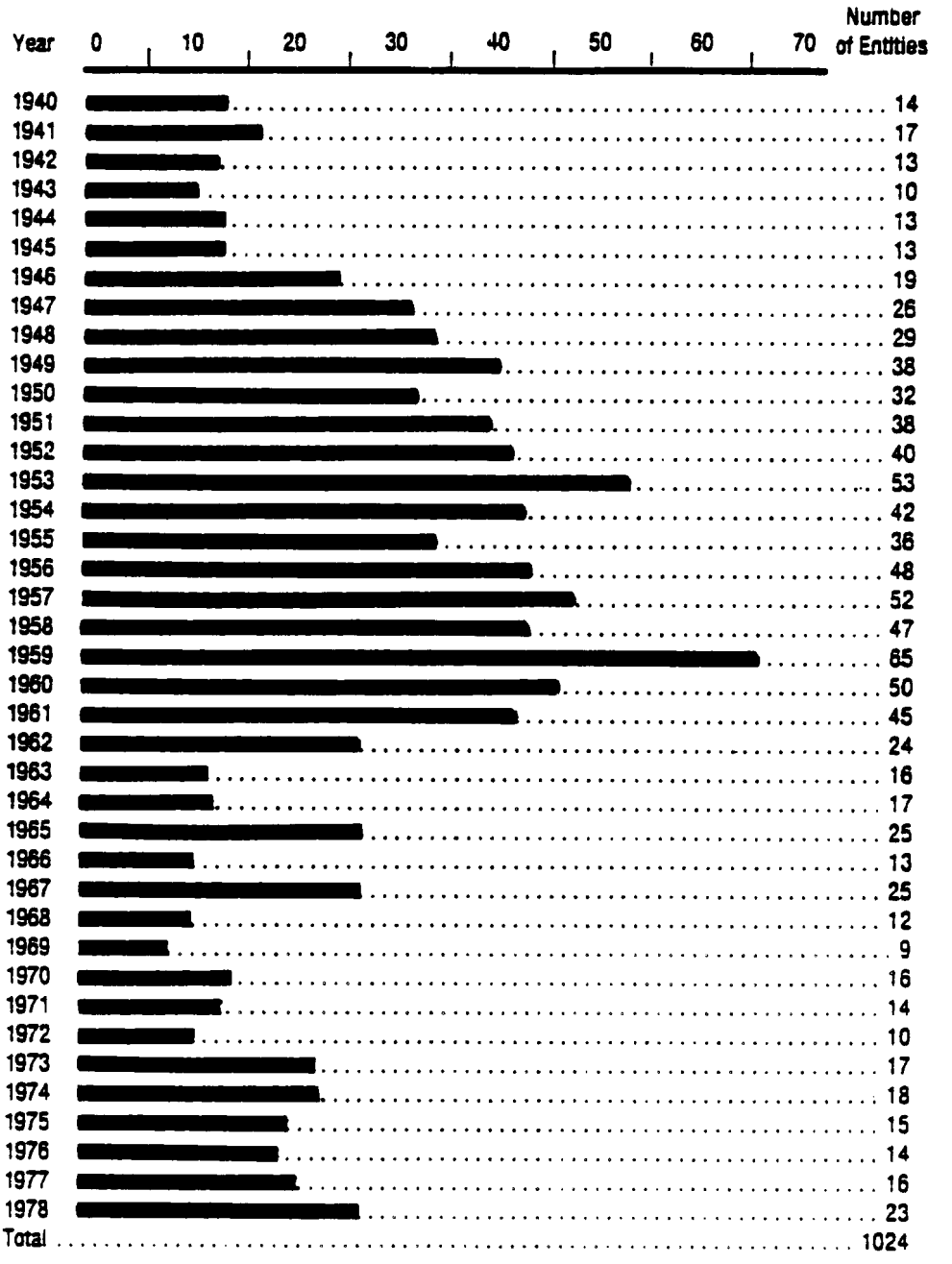
marketed (after NDA approval) in the United States. Figure 4 provides the available data on new drug introductions in the United States from 1940-1978.

It is interesting that in 1966, the United States produced its largest advantage (over foreign firms) in domestic new drug filings (1703 compared with 849). Three years later, those newly patented compounds resulted in only nine new drug introductions (refer to Table IV for mean development times), the lowest marketing output on record.

In fact, following the 1962 Drug Amendments, new American drug introductions have remained at a level significantly below that seen in the 1948-1961 period (see Figure 4).

Further evidence of the impact of foreign patent filings in the United States is provided by the Laubach study. (8:74) Laubach's analysis revealed that of the seven most significant drugs, from an economic point of view, introduced into the United States' market from 1970-1977, five were of foreign origin.

The patent system as it exists in the United States, has always been primarily a product patent system. Although manufacturing processes may be patented, pharmaceutical entities may not be exclusively developed and sold based upon process patents. Use patents provide secondary protection for drug product licenses.




SOURCE: Pharmaceutical Manufacturers Association, Prescription Drug Industry: Pharmaceuticals, Medical Devices and Diagnostic Products - Fact Book 1980 (Washington, D.C.: Pharmaceutical Manufacturers Association, 1980), p. 30.

**FIGURE 4**

**NEW SINGLE ENTITY DRUG INTRODUCTIONS TO US MARKET 1940-1978**

Product patents are granted for a seventeen year period, after which they expire and may not be renewed. This patent system has had a major impact upon pharmaceutical research and development as the number of years required to develop a new product (gain an NDA approval) has grown following the 1962 Drug Amendments (see Table IV above, and Table VI below).

As the number of effective years of exclusive marketing has dwindled, the return on investment (ROI) for new products has also decreased. (2:173) In fact, from 1970-1976, only thirteen of thirty-seven new drugs introduced into the United States' market subsequently covered their research and development costs or made a profit. (2:173)

A study by Grabowski and Vernon found that a product (marketing) life of twelve to nineteen years was necessary (in the United State in 1970-1976), in order to achieve a break-even point in sales vs. investment. (6:181)

These data indicate that regulatory changes which occurred in the United States in the 1960's have resulted in longer drug development, producing shorter (exclusive) marketing lives (9.5 years average in 1979 (7:173) ), and smaller numbers of financially successful drugs.

As a result of these changes, the number of smaller independent firms in the United States has sharply declined. (7:175) Large firms have increasingly sought to diversify

TABLE VI

EFFECTIVE PATENT LIFE OF NEW DRUG PRODUCTS 1966-1978

| YEAR | PATENTED NEW CHEMICAL ENTITIES | AVERAGE EFFECTIVE PATENT LIFE* (years) |
|---|---|---|
| 1966 | 10 | 13.6 |
| 1967 | 16 | 14.4 |
| 1968 | 10 | 13.5 |
| 1969 | 8 | 12.7 |
| 1970 | 14 | 14.4 |
| 1971 | 12 | 12.2 |
| 1972 | 6 | 10.9 |
| 1973 | 12 | 12.1 |
| 1974 | 15 | 13.0 |
| 1975 | 11 | 11.4 |
| 1976 | 15 | 11.3 |
| 1977 | 15 | 9.6 |
| 1978 | 14 | 10.5 |
| TOTALS | 147 | 12.3 |

*17 years minus the average elapsed time for obtaining the new drug approval from the FDA after authorization to proceed with investigational new drug (IND) studies.

SOURCE: Pharmaceutical Manufacturers Association, Prescription Drug Industry: Pharmaceuticals, Medical Devices and Diagnostic Products - Fact Book 1980 (Washington, D.C.: Pharmaceutical Manufacturers Association, 1980), p. 44.

into other related industries to increase their overall return on investment.

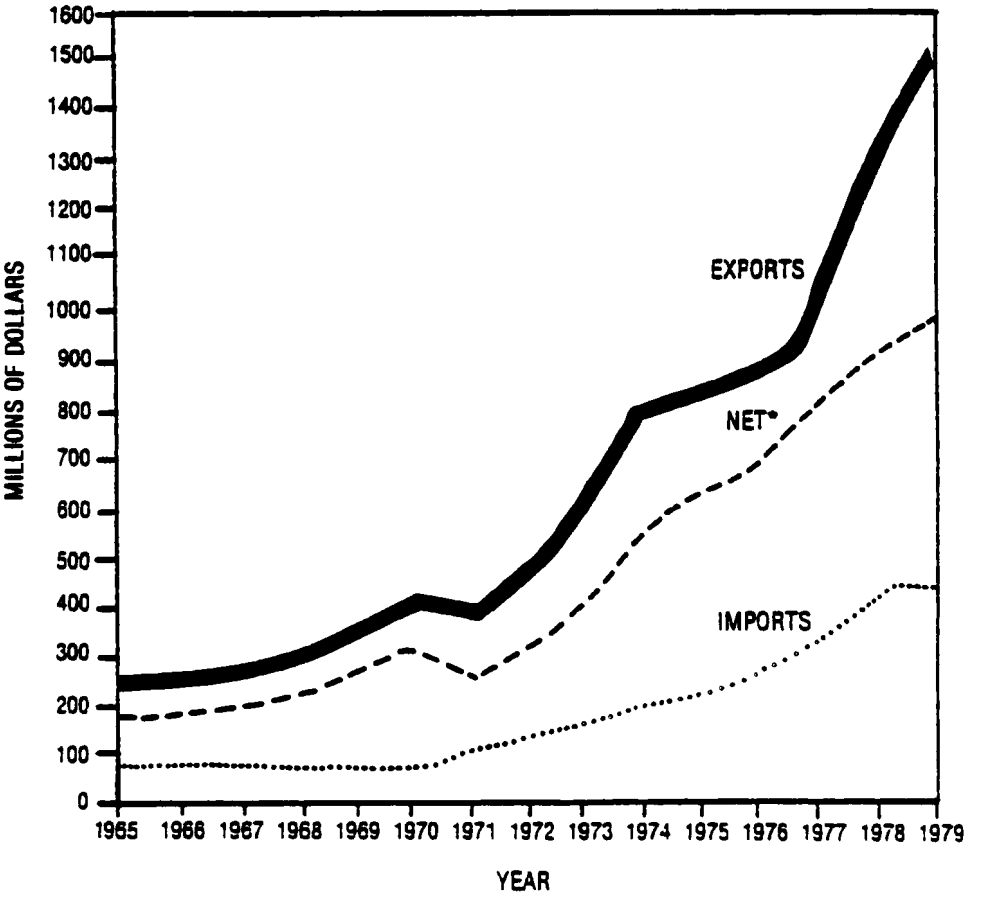
Perhaps the most important result of the changes in the United States' environment has been the movement of research and development to foreign countries. Grabowski has documented the increased percentage of research and development being carried out abroad, based upon increased international sales and more favorable regulatory environments. (9 & 7)

Import and Export of Pharmaceuticals in the United States

The United States' balance of trade in pharmaceuticals has grown steadily since the 1962 Drug Amendments. In the 1960s, drug export to import ratios averaged about three to one (refer to Figure 5). In the 1970s, this ratio rose, reaching four to one by 1979. Translated into dollars, the United States' balance of trade surplus in pharmaceuticals rose from approximately $200 million per year in the 1950s and 1960s to more than $1 billion in 1979. (10:60)

The majority of pharmaceutical exports carried out by American firms have not been finished products. Most shipments have consisted of raw materials and intermediate products. (10:62) This export practice provides significant insight into the American pharmaceutical market when compared with the foreign-based markets.

Multinational expansion of the United States' pharmaceutical industry has increased significantly in the




*Exports minus imports.

SOURCE: Pharmaceutical Manufacturers Association, Prescription Drug Industry: Pharmaceuticals, Medical Devices and Diagnostic Products - Fact Book 1980 (Washington, D.C.: Pharmaceutical Manufacturers Association, 1980), p. 61.

**FIGURE 5**

**US EXPORTS AND IMPORTS OF MEDICINAL AND PHARMACEUTICAL PREPARATIONS 1965-1979 ($ Millions)**

period 1962-1982. In fact, foreign bulk sales by American firms actually exceeded domestic bulk sales in 1979. (11:7) It is not clear whether multinational expansion by American firms was a direct result of greater regulatory and financial burdens. However, sales and export data document the greatly increased emphasis and results of American activities abroad following the 1962 Drug Amendments (refer to Figure 6).

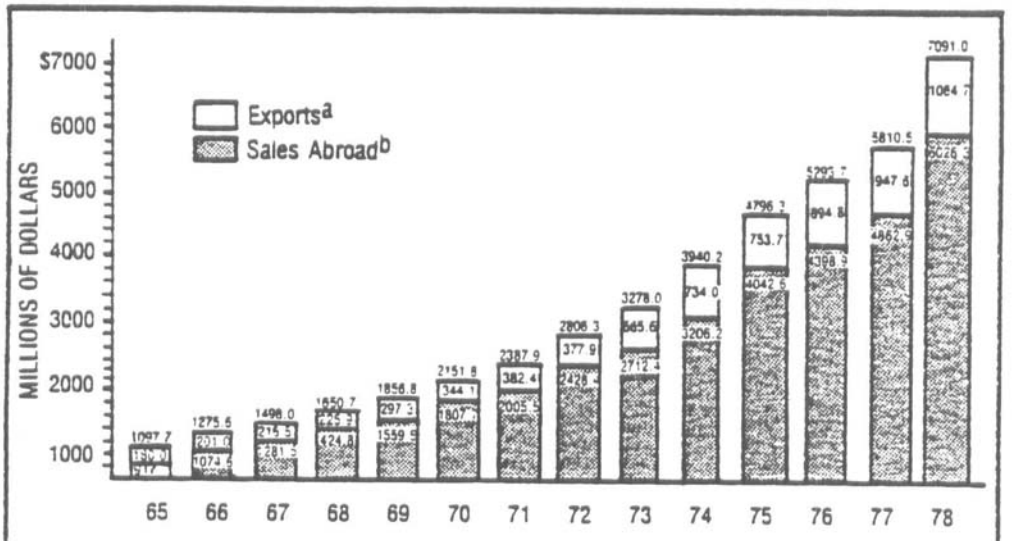
The growth of American export and multinational expansion produced foreign sales which outpaced American sales (in growth) during the 1970's. (10:66) As mentioned above, many of the exported drugs from the United States have taken the form of intermediates (usually penultimate forms) and raw materials. There are a number of important reasons for this, specifically:

1. Foreign subsidiaries require the flexibility to choose final dosage forms based upon local preferences

2. Packaging and laveling must be appropriate to local markets (often in foreign languages)

3. Many countries such as Brazil, Mexico and Italy require local manufacturing of pharmaceuticals, hence the need to import raw materials (excipients) and penultimate active ingredients

4. The United States has prohibited export of drugs not approved by the Food and Drug Administration. (10:62) Multinational pharmaceutical companies regularly avoided this




[a]"Exports" includes shipments to subsidiaries abroad as well as exports to nonaffiliated firms. These are based on ethical pharmaceutical sales as provided by member companies and are not directly comparable with Commerce Department or United Nations trade data.

[b]"Sales Abroad" refers to sales in a foreign area by subsidiaries or other corporate operations, adjusted to eliminate double counting of intrafirm transactions. Also excluded are sales outside the US by foreign-owned firms which have subsidiaries in the U.S.

SOURCE: Pharmaceutical Manufacturers Association, Prescription Drug Industry: Pharmaceuticals, Medical Devices and Diagnostic Products - Fact Book 1980 (Washington, D.C.: Pharmaceutical Manufacturers Association, 1980), p. 65.

**FIGURE 6**

**FOREIGN SALES OF ETHICAL PHARMACEUTICALS BY US FIRMS 1965-1978**

requirement during early development by shipping precursors and penultimates to foreign subsidiaries until those subsidiaries obtained the capability to produce sufficient bulk for local research and development purposes. This step represents a commonly used pathway for drugs discovered in the United States to be developed (first) abroad.

5. Precursor sales to foreign subsidiaries provide a means for transfer pricing. The transfer pricing provides a basis for substantiating higher finished dosage form prices in countries where pricing is government controlled (the European Economic Community with the exception of Germany).

It is clear that regulatory and market forces have spawned American pharmaceutical exports and the subsequent positive trade balance. In addition, the export of early development projects has served to strengthen the leading importers (European countries and Japan), by placing important important new drugs destined for worldwide development in their hands. These foreign countries have, in the last decade, become centers for specific types of drug development studies. Thus, preclinical studies are often simply repeated in the United States years after the initial work has been carried out in France or Japan. This situation appears likely to continue as the world pharmaceutical market expands (especially in third world countries) amid a growing harmonization of regulatory requirements.

## THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984

The Drug Price Competition and Patent Term Restoration Act of 1984 (Act) became effective September 24, 1984. Passage of

this Act was the result of lengthy negotiations which included the research based pharmaceutical manufacturers and the generic pharmaceutical companies,and represented a compromise between the objectives of these two groups. Title II of the Act provides for the extension of patent life for the time lost during the regulatory review process, a goal long sought by the research based companies. Title I of the Act establishes a comprehensive mechanism for Abbreviated New Drug Applications (ANDA's) which allows for approval of generic versions of pioneer products without the need for duplication of the pioneer drug manufacturers' safety and efficacy studies, a goal long sought by the generic industry. Previously, such a system existed only through Food and Drug Administration (FDA) regulations applicable to generic versions of pioneer drug products approved prior to 1962. Summarized below are the major provisions of the Act.

## TITLE II - PATENT TERM EXTENSION

This section of the Act provides for an extension of the patent life for human drugs, food additives, color additives and medical devices[1] to compensate for the loss of patent life resulting from the regulatory review process. For patents

[1]While this portion of the Act applies to all of these products regulated by the FDA, this article will discuss the Act with respect to drugs only.

issued after September 24, 1984, the effective date of the Act, up to five years of extension may be available. For patents issued prior to the effective date of the Act, a patent can be extended for a period of two or five years, depending upon when the Investigational New Drug Exemption Application (IND) was filed.[2] In order to qualify for extension, 1) the patent must not have expired prior to approval of the product by the FDA; 2) it must be the first extension of the patent; 3) a patent application must be submitted within sixty (60) days of the FDA approval of the product;[3] 4) the product must be the subject of a regulatory review period; and 5) the particular marketing of

[2] If the Investigational New Drug Exemption Application (IND) for the product was submitted prior to the effective date of the Act, up to two years of extension may be availabe. If the IND was submitted after the effective date of the Act, up to five years of extension may be available.

[3] One issue that can be somewhat ambiguous under the statute is when a product is approved by the FDA for purposes of filing a timely patent extension application and determining the length of the regulatory period. The FDA has attempted to clarify this issue in recent proposed regulations. The proposed regulations provide that an application is "approved" on the date the FDA notifies the applicant in writing that the application is approved. An approval letter is distinguished from an approvable letter in the preamble to the proposed regulations. An approvable letter is described as one which requires further substantive actions or the supplying of additional information prior to marketing. An approval letter is described in the preamble as one which related only to minor editorial labeling deficiencies. 51 Fed. Reg. 25338, approval for an ANDA of an NCE approved during that time cannot be effective until ten years following the original approval of the NCE. The approval for an ANDA of a non-NCE approved during this time could not have been effective until September 24, 1986.

the product must be the first permitted marketing or use of the product.

The amount of extension available is limited to the "regulatory review period" which, for human drug products, begins when an IND becomes effective and ends on the date the FDA approves the product. Patent extension is limited as follows:

1) only one-half of the investigational phase will be counted in calculating the regulatory review period;

2) the regulatory review period will be reducted by any time the applicant did not exercise "due diligence", as discussed more fully below;

3) the total effective life of the patent after its term is extended cannot exceed fourteen (14) years; and

4) only one patent can be extended for each regulatory review period.

As noted above, the regulatory review period will be reducted by the amount of time an applicant did not exercise "due diligence" which is defined in the Act as "that degree of attention, continuous directed effort, and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period." Legislative history to the Act makes clear that "delays caused by temporary unavailability of necessary testing facilities or a scientific dispute involving tests required for approval or the

interpretation of those tests, are examples of delay which can reasonably be expected to occur and would not be a basis for finding a lack of due diligence."

As part of its application for patent extension, which is filed with the Patent and Trademark Office (PTO), an applicant must describe his activities during the FDA review process. Upon its receipt of an application for extension, the PTO notifies the FDA, which then makes a determination regarding the length of the applicable regulatory review period. The FDA notifies the PTO of its determination and publishes it in the Federal Register. Thereafter, a petition may be filed with the FDA claiming the applicant had not exercised "due diligence" in pursuing FDA approval for the product. Recent proposed regulations set forth procedural rules the agency will follow in making such a determination.[4] Should the FDA conclude that an applicant failed to exercise due diligence during the regulatory review period, such time will be deducted from the period of patent extension.

## TITLE I - ABBREVIATED NEW DRUG APPLICATION (ANDA)

Title I of the Act, which applies to human drugs,[5] establishes a system for Abbreviated New Drug Applications

[4] 51 Fed. Reg. 25338 (1986)

[5] These provisions apply both to prescription drug products and over-the-counter drug products which are regulated as new drugs through the NDA system.

(ANDA's) under which a generic version of a pioneer drug can be approved without duplication of studies demonstrating safety and efficacy, and marketed once a patent has expired for the pioneer drug. Previously, ANDA's were recognized only to a limited extent by FDA regulations. This portion of the Act also provides a system of exclusivity which prohibits the approval of an ANDA for certain periods of time, thereby allowing a period of exclusive marketing of the pioneer product, independent of any patent protection that may also exist.[6]

1. The ANDA system. Title I of the Act sets forth an ANDA system which allows generic versions of pioneer drugs to be approved without the submission of safety and efficacy data. The effective date of such approvals is subject to any existing patent rights for the pioneer product. Examples of popular drugs which are now subject to ANDA's under this new system, include Valium[W] (Roche's diazepam) and Inderal[W] (Ayerst's propranolol hydrochloride).

An ANDA for a generic version of a pioneer product must contain information which establishes that the generic drug has the same conditions of use as the pioneer drug, the same active ingredient(s), route of administration, dosage form and

[6]It should also be noted that the Act puts "paper NDA's" into the same category as a ANDA's. For all practical purposes, it should not make a difference whether a generic drug is approved through a paper NDA or an ANDA.

strength, and that it is bioequivalent to the pioneer drug. The ANDA must also provide for the generic to have the same labeling as the pioneer drug except, of course, for the identification of the distributor or manufacturer. An appropriate patent certification must also be included in the application. With respect to the patent certification, the ANDA applicant must certify that the required patent information has not been filed by the pioneer applicant,[7] the patent has expired, the patent will expire on a specified date, or the patent is invalid and will not be infringed by the manufacture, use or sale of the generic product. In addition, the ANDA must include certain technical information regarding the composition and ingredients of the generic drug, and its method of manufacture.

The Act also provides specific grounds for disapproving ANDA's or withdrawing their approval, including a failure to demonstrate bioequivalence or bioavailability, and the withdrawal or suspension of the pioneer product due to safety or efficacy reasons.

The criteria described above relates to generic products which are the same as a pioneer drug. In addition, the Act provides a mechanism for approving ANDA's for generic products

[7] The Act establishes a system whereby patent information concerning pioneer products is required to be submitted in NDA's and published by FDA.

(including combination products) which are not exactly the same as a pioneer drug. These include products which have a different route of administration, dosage form or strength, or a different active ingredient in a combination product. The Act requires that before an ANDA can be submitted for such a product, a petition requesting permission to file the ANDA must first be submitted by the applicant and approved by the FDA. The petition must show that the generic drug, even though different in some respect from the pioneer, can be approved without the preclinical and clinical investigations required for a pioneer NDA. If this showing is not made satisfactorily to the FDA, the petition must be denied and an ANDA cannot be filed for that generic product.

If the FDA approves the petition, an ANDA can then be filed which must contain all of the basic information described above, as well as certain additional information which pertain to the particular difference in the generic drug. For example, if the generic drug is a combination product and one of the active ingredients is different from that present in the pioneer combination, the ANDA must show that the other active ingredient(s) of the combination are the same as the pioneer and that the generic drug will have the same therapeutic effect as the pioneer drug.

Examples of how the petition process can be used include the potential interchangeability between aspirin and acetaminophen

in certain combination drug products. The FDA has approved changes in antihistamine/decongestant ingredients present in combination controlled release products based upon their classification as category I in an OTC monograph. The Agency has also approved changes in dosage form, e.g., propranolol Hcl and diazepam tablets to oral solutions, ibuprofen tablets to capsules. Examples of changes in strength that the FDA has approved include a change from a 5 mg./ml. nitroglycerin IV solution to a 10 mg./ml. nitroglycerin IV solution.

2. Exclusivity. The exclusivity provisions of the Act provide further incentive for research based companies to conduct research on new products or new indications. Under these provisions, an ANDA may not be approved for a generic product for specified periods of time following the approval of the pioneer NDA (or supplement). These exclusivity provisions apply to new products, as well as new indications or uses for existing products. The exclusivity provisions make a distinction between a "New Chemical Entity" (NCE) and a non-New Chemical Entity (non- NCE). An NCE is a drug, no active ingredient of which has been approved before in any full NDA.

The periods of exclusivity are as follows:

1. NCE. An ANDA for a generic version of an NCE which was approved after September 4, 1984, the effective date of the Act, cannot be submitted to the FDA for five years after the original NDA was approved for the NCE. (There

is an exception for ANDA's which challenge the validity of the pioneer patent. In that case, the ANDA can be submitted after four years.)

2. Non-NCE. The approval for an ANDA of a generic version of a non-NCE cannot be effective for three (3) years after the date a pioneer NDA or supplemental NDA was approved for the non-NCE. This, of course, means that unlike an ANDA for an NCE, an ANDA for a non-NCE can be submitted during the period of exclusivity. The approval may not be effective, however, until the period of exclusivity has expired.

3. Transition Rules. There are also transition rules for pioneer products approved from January 1, 1982 through the effective date of the Act, September 24, 1984. The approval for an ANDA of an NCE approved during that time cannot be effective until ten years following the original approval of the NCE. The approval for an ANDA of a non-NCE approved during this time could not have been effective until September 24, 1986.

Exclusivity is available only if the pioneer applicant conducted or sponsored clinical trials, other than bioavailability studies, which were essential for approval of the NDA or supplemental NDA.[8] It is also important to note

[8]The only exception to this requirement was for non-NCE's approved from January 1, 1982 until September 24, 1984.

that exclusivity applies both to patented and unpatented drugs. For a patented drug, the period of exclusivity runs concurrently with the patent; therefore, depending on the term of the patent, plus any extension, the exclusivity provisions may or may not add an additional period of protection.

The foregoing has been a brief and general overview of a long and very complicated statute. It is certainly the most significant legislation affecting the pharmaceutical industry since passage of the 1962 amendments to the Food, Drug and Cosmetic Act. Because of the significance of this Act, its provisions must be considered in the day-to-day decisions of drug development and planning.

## III. NDA REWRITE - ANALYSIS AND IMPLICATIONS

The revised regulations governing the approval for marketing of new drugs and antibiotics (NDA Rewrite) are intended to improve the efficiency of FDA's approval process, thus decreasing the time needed by the Agency to review applications, while improving the already high level of public health protection provided by FDA. The preamble of the regulations state that these improvements will help applicants prepare and submit higher quality applications and permit the FDA to review them more efficiently and with fewer delays. The objectives of the NDA Rewrite final rule are to establish an efficient, but thorough, drug approval process in order to both

(1) facilitate the approval of drugs shown to be safe and effective; and (2) to ensure the disapproval of drugs not shown to be safe and effective.

This final rule (the NDA Rewrite) was originally proposed on October 19, 1982 and completes the first phase of efforts by the Department of Health and Human Services to revise regulations governing the new drug approval process. The second phase of these regulatory revision efforts will cover regulations governing investigational drugs (NDA Rewrite) which were proposed in the Federal Register on June 9, 1983. The second phase is nearing completion and final regulations will be published in the future. A third phase involves noncodified guidelines on application format and on fulfilling testing requirements.

## Highlights of the Final Rule

The final rule is a comprehensive document, consisting of over 300 pages. The listing of major topics affected by the revised regulations follows:

- Content and format of applications
- Safety updates to original applications
- Case report forms and data tabulations
- Foreign data
- Adequate and well-controlled studies
- Time frames for review of applications by FDA and responses by the applicant

- Communications between FDA and the applicant
- Dispute resolution
- Postmarketing reporting of adverse drug experiences
- Supplements to approved applications

The Sections of this paper that follow provide in-depth discussions of the revised regulations. One primary goal of the NDA Rewrite was to accelerate and make more efficient the review process involved in approving new drugs for human use. In order to expediate drug approvals, the Act seeks to help applicants submit an application of higher quality and of more uniform content, resulting in more rapid and efficient FDA review. A shorter review time would benefit both the consumer and the applicant by insuring that the drug would be available earlier to the public, thus helping research intensive firms achieve necessary profits.

The new regulations have been in effect since May 13, 1985. (19) This legislation is part of a larger effort by the FDA to reaccess all facets of the agency's drug approval process. The reaccessment process on the part of the FDA has been a necessary response to new limitations on the agency, prompted by the Federal Budget Balancing act (Gramm - Rudman).

The NDA Rewrite outlines content and format changes to enhance the efficiency of the agency's review. Section 314.50 of the NDA Rewrite requires the submission of two copies of the new drug application (NDA). These are, the archival copy and

the review copy. (20) The archival copy and the review copy are identical, but the use of each is different.

The archival copy is the official record of the NDA and is kept permanently on file at the FDA (21). The archival copy can be submitted in microfiche form. (22)

The review copy is used by FDA personnel as a working copy. This copy makes possible concurrent review of the five or six technical subsections of the application by various departments at the FDA. These sections are specifically: Chemistry, Manufacturing and Controls, Non-Clinical Pharmacology/Toxocology, Human Pharmacokinetics and Bioavailability, Clinical Data, and Microbiology (Anti-Infective Drug Products). Each technical section is required to contain data and information in sufficient detail to permit the FDA to make an evaluation as to the safety and efficacy of the drug. This move to concurrent reviews was designed to speed up the overall review process of the NDA. (23)

In addition to concurrent review, the FDA now permits presubmission of the chemistry, manufacturing and controls section of the NDA 90 to 120 days prior to the full NDA submission, in order to expediate review and permit early resolution of deficiencies. FDA's ability to review sequential submissions will depend upon available resources (324.50). Historically, it has been this section which most often caused delays in the NDA review process. Allowing presubmission of

this section is an attempt by the FDA to overcome these delays. (24)

The FDA has made these submission changes in an attempt to provide, (as has the European Economic Community) a more uniform format for the application process. (25)

In the United States, the NDA Rewrite intends to provide uniformity and ease in the review process by requiring an overall summary of the application. This major change in the NDA Rewrite is intended to decrease the review time for an NDA (New Drug Application). This summary accompanies each of the various technical subsections and provides individual reviewers with a compendium of information about the drug product. The overall summary must discuss all aspects of the application and synthesize the information into a well-structured and unified document. The summary should be written in the same detail required for publication in, and meet the editorial standards generally applied by, scientific and medical journals. The length of the summary will vary according to the nature of the drug. Data in the summary should be presented in tabular and graphic forms whenever possible. The summary should include critical details of study design, sufficient numerical data to provide a quantitative understanding of the data, and a forthright discussion of any problem areas.

The summary is intended to facilitate review of the application. The revised regulations regarding the NDA summary

spell out in more detail than is provided in the previous regulations, the information the agency will require. The NDA Rewrite does not specify the length of the overall summary. However, the average summary should be approximately 50 - 200 pages in length. A complete explanation of the intended labeling of the drug product should also be contained within the overall summary. This information should help to avoid the confusion which in the past has lead to marketing disputes of labeled drug products.

Pharmaceuticals, which have been previously marketed in other countries before FDA approval, must now include a "marketing history" of the drug. This history should include information which will support the clinical section of the application. In addition, the history should describe in full every indication for which the drug is being used. Finally, the "marketing history" must contain a list of every country the drug is being presently marketed in and the length of time the that drug was available to the public. The applicant must also provide a complete listing of pending applications for approval of the new drug, and in what countries those applications are being reviewed. Detailed information on any withdrawl of the drug from the market for reasons related to safety and efficacy must be reported.

Chemistry, Manufacturing and Controls Section

In this section of the final rule, the FDA no longer requires detailed information about the identity, strength,

quality and purity of the active drug substance if compendial standards are met, i.e., National Formulary, U. S. Pharmacopea, and Current Good Manufacturing Practices. Any active drug substance not defined by these compendial standards (such as new chemical entities) would be subject to full specifications. (26)

Non-Clinical Pharmacology/Toxicology Section

The FDA now requires in this section of the NDA Rewrite that all pharmacological actions of the drug be defined. This differs from past submission requirements which necessitated only information concerning the pharmacological actions relevant to the primary indication being sought. The FDA now requires complete information about pharmacological action, in an attempt to gain wider understanding of the new drug's effects, including side effects and drug interactions. (27) The Non-Clinical Pharmacology/Toxicology section of the application in regard to individual animal data wi11 remain unchanged. Full tabulation of individual animal data from long-term toxicity and carcinogenicity studies are still required to be submitted. Compliance with GLP (Good Laboratory Practices) regulations applies to Non-Clinical safety studies (21 CFR 58.3(D)). Comparison of human pharmacology studies with animal pharmacology and toxicology now must be included in the NDA.

Human Pharmacokinetics and Bioavailability Section

All pharmacokinetic parameters, i.e. (Vd, t 1/2, kel, etc.) must be defined, in addition to the bioavailability

characteristics of the drug in this section of the NDA. The FDA requires that a brief description of the protocol be outlined in this section of the NDA, and should include the following: study design, objectives, and the analytical and statistical methods to be used. (28) A statement concerning whether or not the study was conducted in compliance with institutional review board regulations must be included. In any new NDA, specifications for the dosage form must include tests to assure bioavailability of the dosage form. The FDA has retained the current requirements for the submission of bioavailability data as described in 21 CRF 320.21-320.30.

Clinical Data

In this section of the NDA Rewrite, the final rule retains the substance of the previous requirements, but are presented in more detail. The requirements for this section are listed below. Discussion of new requirements for the clinical data section immediately follows.

The following are to be included in the clinical data section:

(i) Description and analysis of each clinical pharmacology study.

(ii) Description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study.

(iii) Description of each uncontrolled clinical study and a summary of results.

(iv) Description and analysis of other data relevant to an evaluation of safety and efficacy, including foreign data, commercial marketing experience, published literature, unpublished scientific papers.

(v) Integrated summary of data demonstrating substantial evidence of effectiveness for the claimed indication.

(vi) Safety summary and updates.

(vii) A description and analysis of studies related to abuse of the drug (if applicable).

(viii) Integrated summary of the benefits and risks of the drug.

(ix) Statements re: compliance with institutional review board and informed consent regulations.

Discussion of New Requirements for Clincial Data

A. Clinical pharmacology

1. The regulations now specify that clinical pharmacology studies be analyzed. (This may need to be clarified.)

2. The final rule requires a brief comparison of the human (pharmacology) studies with the animal pharmacology and toxicology data. This requirement

is intended to provide an examination of the clues to potential usefulness or toxicology in humans provided by animal data. The human results should thus be compared to all pertinent animal observations.

B. Controlled clinical studies

1. If a study report is an interim analysis, this is to be noted and a projected completion date provided.

2. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., discontinued or ongoing/incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

C. Uncontrolled clinical studies

Analysis of these studies is not required. However, a brief statement explaining why the study is classified as uncontrolled must be included. This will enable the Agency reviewers to determine what conclusions can be validly drawn from these studies.

D. Other data or information

Other data or information relevant to an evaluation of the safety and effectiveness of the drug applies to any information

obtained or otherwise received by the applicant from any source, foreign or domestic. This includes:

1. Foreign clinical data which would require analysis.
2. Controlled and uncontrolled studies of uses of the drug other than those proposed in the application. Some analyses of controlled studies not pertinent to the proposed uses of the drug would be required.
3. Commercial marketing experience.

   (The implication in the regulations that analyses of commercial marketing experience, reports in the scientific literature and unpublished scientific papers would be necessary needs clarification.)

E. Integrated summary of efficacy data for claimed indications.

Evidence is required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

F. Integrated summary of all available information about the safety of the drug product.

1. This summary is to include pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions

and other safety considerations, such as data from epidemiological studies of related drugs.

The Agency does not believe that information about related drugs, such as epidemiologic data, can be ignored in evaluating a new drug. An applicant developing a new member of an already established drug class usually is, and should be, conscious of the experience with other members of the class. Such information may be relevant to labeling and may help focus the evaluation of the data submitted. FDA does not believe that the requirement will be applied unreasonably.

2. A description of any statistical analysis performed in analyzing the safety should be included, unless such analysis is already included in the controlled clinical studies section.

Case Report Forms/Tabulations

Section 314.50 of the NDA rewrite deals with the revised regulations concerning case report forms and tabulations. The new regulations significantly reduce the amount of supporting information applicants are required to submit in an application by no longer requiring the routine submission of copies of most case reports. Instead, the FDA will require the submission of tabulations of the data in the case reports. The tabulations are prepared by the drug sponsor and contain the very same numbers as the case report forms in which they are

based, and the data are clearly identified by individual patient. Thus, tabulations are ordinarily a more concise and efficient presentation of the data contained on the case report forms.

Applicants are encouraged to meet with FDA officials before submitting an application to discuss modes of data presentation and possible omission of certain data contained in case reports. Verification that the tabulations of data are accurate and complete is absolutely critical.

Although case reports will not have to be routinely submitted for all studies, they must be readily available in an organized manner for all studies prior to submission of the application. Response, within 30 days, to an FDA request for additional data is critical.

Foreign Clinical Data

The new NDA rewrite now allows data from foreign clinical trials to be submitted as a basis for proof of efficacy. This is a significant change and has far reaching implications. Foreign clinical trials are now acceptable only if the trials are performed to U.S. Standards.(31) Specifically:

1) The foreign data are applicable to the U.S. population and U.S. medical practice.

2) The studies have been performed by clinical investigators of recognized competence.

3) The data may be considered valid without the need for an on-site inspection by the FDA or, if FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. (32)

4) All foreign clinical study reports will now require statistical analysis.

5) If foreign data is to be accepted as evidence of safety and efficacy: a) all case reports must be available, b) case report data must be tabulated to U.S. standards, c) studies must be conducted in accord with the Helsinki Declaration.

6) Studies must be adequate and well-controlled.

This change from past regulations will most certainly expediate the ever increasing movement of the pharmaceutical industry's research from U.S. centers to foreign sites. Section IV of this paper contains a thorough discussion of likely impacts of this portion of the NDA Rewrite.

Although there are newly stated requirements for data intended to be the sole basis of U.S. marketing approval, these requirements are in addition to, and not in place of, the current requirements stated under existing 312.20 for any foreign clinical data intended to support U.S. approval, whether or not it is intended to be the sole basis.

Current subsection 312.20 lists the bases for acceptance for foreign clinical data and these requirements will be maintained under new 314.106. Subsection 312.20 states the FDA will consider "detailed information resulting from those studies performed abroad which are well-conceived, well-controlled, performed by qualified experts and conducted in accordance with ethical principals acceptable to the world community". Thus, the key criteria for acceptance of foreign clinical data in support of U.S. NDA's are "Adequate and Well-Controlled studies". Therefore, subsection 314.126 on Adequate and Well-Controlled studies is equally applicable to clinical studies conducted both in the U.S. and abroad.

Section 314.126 of the NDA Rewrite outlines the study design characteristics FDA considers necessary for investigations to provide the primary basis for determining whether there is substantial evidence to support the claims of effectiveness for new drugs and antibiotics. These study design characteristics are applicable to any study, wherever conducted, which is intended to provide substantial evidence of effectiveness.

The principal difference, in the new regulation and of utmost importance, is that whereas the current 314.11 states that an active treatment control may be used to demonstrate efficacy, the new regulation (314.126) states that the mere demonstration of similar effectiveness of an active control and

investigational drug can mean that, either both drugs are effective or both are ineffective. (In actuality, for several years FDA has been discouraging use of active control studies for purposes of documenting efficacy). Should such a study be conducted, the report should explain why the drugs should be considered effective.

Subsection 314.126 states that an adequate and well-controlled study has the following characteristics:

1) There is a clear statement of the objectives of the investigation and the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

2) The protocol for the study and report of results would describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i) Placebo concurrent control, which usually includes randomization and blinding of patients or investigators, or both.

(ii) Dose-Comparison concurrent control, which usually include randomization and blinding of patients or investigators, or both.

(iii) No treatment concurrent control. Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) Active treatment concurrent control. The test drug is compared with known effective therapy where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. Active treatment trials usually include randomization and blinding of patients or investigators, or both. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective.

(v) Historical control. Historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied.

4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug.

5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysis of the data.

6) The methods of assessment of subjects' response are well-defined and reliable.

7) The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of the test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

8) The Director of the Center for Drugs and Biologics may, waive any of the criteria of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study.

9) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

10) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the drug.

Adverse Drug Reaction Reporting

The second major area in the NDA Rewrite attempts to enhance drug surveillance by changes in adverse drug reaction reporting requirements. These changes were in large part prompted by the problems surrounding the introduction of Oraflex and Selacryn (33) and are intended to permit the FDA to monitor more closely the adverse reactions of drugs during the review period and the early marketing stage. (34) These changes in the NDA will significantly impact industry resources.

Specifically, safety update reports must be sent to the FDA three months after NDA submission, upon receipt of an approvable letter, and quarterly for the first three years of marketing. These safety update reports must include safety data from foreign clinical studies and foreign commercial experience Adverse Drug Reactions.

The new adverse drug reaction reporting requirements are intended to improve communication about adverse drug reactions during the critical period of late drug development and early

marketing. Classifications of adverse reactions include the following:

A) Serious adverse drug reaction

A life threatening or permanently disabeling reaction which requires inpatient hospitalization or requires prescription drug therapy. In addition, death, congenital anomoly, cancer or overdose would always be considered serious. (35)

B) Nonserious drug reaction -- all others

C) Unexpected (Unlabeled) drug reaction

An adverse drug reaction not listed in the current labeling for the newly approved drug. This includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. (36)

D. Expected (Labeled) drug reaction

An adverse drug reaction that appears in the current product labeling. (37)

E) Increase in Frequency

An absolute increase in the number of reports of an adverse drug experience received during a specified time period compared to the number of similar adverse drug experience reports received during an equivalent time period in the past. (38) This is

defined specifically as at least a doubling of the rate of a specific Adverse Drug Reaction.

When determining frequencies, two methods of calculation are available: the Arithmetic, and the Poisson (the distribution of rare events). With rarely occurring adverse drug reactions, the arithmetic calculation tends to underestimate the frequency of adverse drug reactions. As the number of adverse incidents increases, the Poisson calculation will tend to underestimate the frequency. (34)

In the event of a "Serious and Unexpected" (Unlabeled) adverse drug reaction, the F.D.A. must be notified within 72 hours, and followed by the appropriate written form (Form FDA 1639) within 15 working days. (40) This requirement pertains to marketed drug products. If the adverse drug reaction is "Serious and Expected (Labeled)" and occurring with significant increases in frequency, a narrative form must be sent to the F.D.A. as soon as possible, but in any case within 15 working days (the FDA 1639 is the appropriate written form) (41). The narrative must include the time period in which the increase in frequency occured, the method of analysis and an interpretation of the results. Following NDA approval, all adverse drug reactions of a "Nonserious and Expected (Labeled)" nature need to be reported as a part of the safety update reports on a quarterly basis using the FDA 1639. This holds true for Nonserious and Unexpected (Unlabeled)" adverse drug reactions

as well. Quarterly reports continue for three years following approval of the drug, and at annual intervals thereafter. The F.D.A. may also extend the three year quarterly reporting period based on the history of the adverse reactions to date. Each quarterly report is required to contain a narrative summary and complete analysis of the information, as well as frequency calculations. (42)

Time Frames for Review of Applications by FDA

Another major area of the NDA Rewrite deals specifically with the time clocks under which the FDA must now review submissions.

With the sumbission of an NDA, the F.D.A. has 180 days in which to issue an action letter. The action letter can contain one of three decisions:

A) Approval -- Only an approval letter grants permission to market a drug. This letter will be issued when the only deficiencies in the application concern editorial or other minor changes in the labeling. (43)

B) Approvable -- The FDA intends to approve the application if the applicant submits the requested data or information. This letter does not preclude the FDA from re-examining any part of the application. (44)

C) Not Approvable -- the FDA is obligated to refuse an application if it believes that the facilities and controls are inadequate or the information in the application is

insufficient to determine that the drug is safe and effective for the use intended. (45)

The F.D.A. may also refuse to approve an application if bioavailability and bioequivalence data do not meet the requirement of part 320 of the NDA Rewrite. (46)

Issuance of these actions letters can best be understood by looking at the two time tables which govern the final approval of the drug after its initial submission. There are two 180 day time tables, one is for the review of the NDA, and the other is for the filing of the completed NDA (47). The F.D.A. suggests that the applicant focus on the "review clock". This period of time is the actual time from initial receipt of the NDA application to the time when an action letter is issued. The second 180 day period (or the "filing clock"), starts on the 60th day after receipt of the NDA and is important only when the drug company receives a "Not Approvable" action letter, and wishes to litigate the decision by the FDA. This "filing clock" is the time period over and beyond the actual review time, and is used predominantly for dispute resolution. (48)

Although the F.D.A. recognizes the potential for confusion, it believes that the use of "two" time clocks are necessary and not unduly complicated. The "filing clock" requires FDA within 180 days of "filing" of an application, either to approve the application or to issue a notice of

opportunity for hearing.(49) Again, the applicant should rely on the 180 day "review clock" as the measure of review time regarding a NDA.

As in the past the "clocks" may be extended by mutual agreement or by submission of a major amendment. Amendments to the NDA made by the drug company, either on its own initiative, or upon request by the F.D.A., are major causes for an extended review period. A significant change has been made in regard to an extended "review clock" in the NDA Rewrite. Previously, any substantiative amendment to an NDA under review could result in a 180 "restart of the review clock." The new regulation limits the extension to the time required for review of the submission -- with a 180 day maximum. (50) If the FDA requests additional case reports and/or tabulations, the sponsor has 30 days in which to respond. Failure to meet this requirement can result in the FDA classifying the eventual submission as "major" and can extend the review period accordingly. (51) The guidelines for extension are as follows:

| | |
|---|---|
| Chemistry | 0-60 days |
| Pharmacology | 30-60 |
| Case Reports/Tabulations | 0-180 |
| Clinical Studies | 60-90 |
| Biopharmaceutics | 60-90 |
| Statistics | 60-90 |
| Non-Major Amendments | 30 |

Amendments to different disciplines will run concurrently, while amendments to the same discipline are additive. (52) The submission of a major amendment, whether at the initiative of the applicant or in response to a request from FDA, constitutes an agreement by the applicant to extend the date by which the FDA is required to reach a decision on the NDA. Under the new regulations, the agency may not extend the review period more than 180 days. Examples of major amendments which may extend the review period to 180 days are ones that contain significant new data from a previously unreported study or detailed new analyses of previously submitted data.

The 180 day review period is now codified, it has been a statutory requirement since 1962 (but totally ignored by the FDA). The codification in the regulations will probably have little impact on the review process.

With the recent introduction of Gramm-Rudman in March, 1985, the F.D.A. was forced to lay-off hundreds of employees in order to follow cost containment regulations. This bill will have major influences on the "review clock" and undoubtedly increase the review period beyond the current average time period of 27 months. With the enormous cutback of FDA employees, the man-power required to review major amendments to a NDA will be insufficient. The intentions made by the FDA with the submission of the NDA Rewrite to accelerate and make more efficient the review process for new drugs in development

has, for practical purposes, been negated by Gramm-Rudman. FDA is clear in their intent to expediate the approval process by revising the regulations governing the approval of new drugs and antibiotics. The question of whether the regulations will substantially produce a quicker review, when nothing has been changed within the Agency to permit such, remains to be answered. The revised regulations do not significantly affect or change the drug development process per se. The content and format of an application has been changed, the overall result of which will be an increased demand on company resources. Also an increased demand will be placed on Drug Regulatory Affairs groups in the timeliness in which responses to action letters will need to take place. The new regulations for postmarketing reporting of adverse drug experiences and safety update reports will have a significant impact. The requirements for acceptance of foreign clinical data as the sole basis of approval will have significant impact on U.S. pharmaceutical firms in relation to international collaboration. The NDA Rewrite provides no relief for the pharmaceutical industry in relation to regulatory compliance.

## IV. The Future Impact of U.S. Regulatory Changes on Drug Development - Where Do We Go From Here?

Substantially, the impact on drug development brought about by the Waxman/Hatch Act and the NDA Rewrite will not be

felt until the period of 1990-95. Within that time frame, multi-national pharmaceutical companies will begin, in earnest, to submit NDA's based solely on foreign clinical data, carryng out primarily marketing (clinical) studies in the U.S. This approach to drug development will be mandated because of its specific allowance under the NDA Rewrite, and as well, because studies can be undertaken sooner and carried out cheaper ex-U.S. (Europe for example). FDA will be forced to consider these submissions, in spite of their current phylosophical disagreement.

By 1995, the patent entension provisions of Waxman/Hatch will begin to blossom into additional years of marketing exclusivity for a number of drugs in the discovery phase in 1984 (assuming an average development time of 10.5 years). At that time, real patent life in the U.S. may approximate 11-11.5 years. As this occurs, the marketing life for new drugs in the U.S. will become competitive with those in Europe (20 year patents) and Japan (15 year patents plus 6 years of marketing exclusivity for Japanese based firms or subsidiaries) today.

There is little doubt that the European and Japanese authorities will take further steps to enhance real patent life periods, in order to maintain their edge over the U.S as more attractive markets. Although the major impacts of the NDA Rewrite and the Waxman/Hatch Act are substantial in terms of bottom line (R.O.I.) improvements to multinational

pharmaceutical firms, these regulations fail to effectively shift the balance for drug development to a more U.S. based activity.

This outcome is neither good or bad. World health certainly needs to be the ultimate goal, from a regulatory point of view. From a public (world) health perspective, these recent regulatory changes certainly contribute to cost containment, which allows more individuals to avail themselves of drug therapies. The ANDA provisions of the Waxman/Hatch Act is critical to the broader availability of inexpensive generic drug therapies..

On the other hand, the patent extension provisions of the Waxman/Hatch Act provide R.O.I. incentives to the pioneering drug firms. These incentives are truely necessary, in order to insure continued investment in new drug discovery/development, which is a basis of medical (therapeutic) progress.

The NDA Rewrite is unlikely to result in a shortening of regulatory review time for (NDA) submissions to F.D.A. The Gramm-Rudman Act virtually assures a counter balancing of the N.D.A. Rewrite directives in this area. In fact, since 1984, F.D.A. staffing has already declined almost 20%. There is nodoubt, however, that the N.D.A. Rewrite provision place a much greater burden upon the drug regulatory arrairs departments of pioneering drug firms. As a result, it seems likely that N.D.A. submission preparation will take about 50%

longer (up to about 1 year) and require proportionately more staffing to accomplish.

Seen in perspective, these regulatory changes are consistent with others made by the Reagan Administration which seek to shift the societal burdens away from the federal government towards the private sector. The result, of course, will be increased costs of new drug therapies to consumers who can afford them. The impoverished in our society, quite likely will continue to be relegated to inexpensive generic treatments. The gap in this area will rise.

Finally, drug development ex-U.S. will continue to grow as pioneering pharmaceutical firms begin to take a more goecentric view (53) of the drug development process.



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