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POSTMARKETING SURVEILLANCE OF DRUGS:
An Overview of the Need and the Methodology.

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INTRODUCTION

In the words of W.H.W. Inman, " ... no drug with any worthwhile therapeutic activity is entirely risk-free" (1). Drugs by design are intended to modify physiological functions and as such possess the ability to do harm. Additionally, few drugs are specific for their intended effect. Most drugs have some adverse effects. These may or may not be related to the pharmacological action of the drug and may or may not be dose related. Owing to the complex and sometimes idiosyncratic nature of drug action, and to the inevitable limitations of premarketing tests, the adverse effects may not be known at the time of marketing. Thus, the full spectrum of a drug's action (adverse and beneficial) may only be confirmed several years after a drug is first marketed, after it has been used for an extended period of time in a heterogeneous population.

In order to minimize the harmful effects of drugs that are used in an appropriate and therapeutic manner, drugs must be monitored continuously from the time they are first introduced to the market. To function effectively, this postmarketing surveillance (PMS) of drugs should monitor for adverse reactions and ensure that the nature, severity and incidence of known ADRs as outlined in the package insert matches what is observed in clinical practice. It needs to identify previously unknown ADRs as well as identify any factors that may predispose individuals to the adverse effects, including the co-administration of specific drugs. Thus, clinical experience with the drug must be used to continuously reassess the drug's risk-benefit ratio and if necessary enable appropriate remedial action to be carried out. This may include for example, a modification of the labeling or at the other extreme, complete removal of the drug from the market. Finally, an information network needs to be in place that will rapidly communicate important findings of the various PMS activities the medical community.

This paper will review the limitations or blind spots of existing premarketing drug evaluations and also the various methods that are presently used to assess the safety of, and risks posed by marketed drugs.

A. LIMITATIONS OF PREMARKETING EVALUATIONS

The safety and efficacy of few, if any, products are subject to the same amount of regulatory scrutiny as drugs. It is estimated that the height of the documentation paper now required for the approval of a new chemical entity in the initial markets, approaches that of the Eiffel Tower (300.5 meters) (2). The research phase of the drug discovery process may take up to 10 years and the development phase up to 11 years (3). Overall it has been estimated that the cost of developing a new drug in the 1980s is $125m (4).

In spite of these extensive premarketing studies, at the time of initial marketing, only a fraction of a drug's full toxicity profile, and indeed spectrum of pharmacological effects, may be known. Human safety and efficacy data are limited to extrapolations of preclinical toxicity data derived from laboratory animals and on data derived from clinical trials in humans. Although these studies have been effective in

the most part in preventing potentially toxic compounds from gaining access to the market, experience has shown that these tests cannot be relied upon to identify all adverse effects that may be observed after marketing. The major limitations of these premarketing studies are outlined below.

1. Preclinical Animal Studies

Preclinical toxicity studies are carried out to study the functional and morphological effects of the drug in laboratory animals. Generally, acute studies are used to determine whether or not a drug is sufficiently safe to be tested in humans, while chronic studies are carried out to study the long-term effects of the drug. The nature and duration of the chronic studies depends on the proposed pattern of use of the drug and may involve carinogenicity, teratogenicity and mutagenicity testing. Data from these tests are used to support the approval of the drug by assuming that the pharmacokinetics and the pharmacodynamics of the drug are the same in both laboratory-animals and humans. However owing to inter-species differences, this assumption may be invalid. Accordingly, a drug that produces negative findings in laboratory animals may produce serious adverse affects in humans.

For example, preclinical toxicity studies carried out on practolol, indicated that the drug was safe and well tolerated. It's LD_{50} in animals was found to be approximately twice that of propranolol. Practolol was withdrawn from the market after approximately five years of marketing, after clinical experience revealed it to have unacceptable human toxicity (5). Moreover, even after the subsequent characterization of the human lesions, it was not possible to reproduce the toxicity in laboratory animals (6). In other cases, preclinical toxicity studies may underestimate the incidence and/or severity of human adverse effects. Clearly, preclinical toxicity tests cannot be relied upon to provide unequivocal evidence regarding a drug's action in humans.

2. Premarketing Clinical Studies

It is unrealistic to expect clinical trials to identify all possible effects of a drug since they can never reproduce the pattern of drug usage experienced after marketing. The primary limitation of clinical trials lies in the number of patients studied, the duration of exposure of the patients to the drug and the characteristics of the patients involved.

Generally between 500-3000 patients are exposed to an experimental drug during the premarketing clinical trials. Yet, in order to have a 95% certainty of detecting a reaction that has an incidence of 1 in 1,000 and which is unique to the drug, over 3,000 patients would have to be exposed to the drug (7). If the event were not specific to the drug but also occurred in its absence, an even greater number of patients would be required. The actual number would depend on the spontaneous background incidence of the event (Table 1). Thus, clinical trials are able to detect only relatively common ADRs i.e. those which occur at rates of greater than 1 in 1000 and which are specific to the drug. Furthermore, it is clearly impractical and not economically feasible to design trials with improved sensitivities.

Patients are enrolled in premarketing trials for only a limited amount of time. Frequently, patients are exposed to the drug for a maximum period of about 12 to 24 months. Thus, clinical trials are incapable of detecting ADRs that require long exposure periods. For example the various manifestations of practolol's oculomucocutaneous syndrome required an average of 24 months of treatment and practolol-induced sclerosing peritonitis occurred after an average of 34 months treatment (5). Nor can clinical trials detect ADRs which have long latency periods such as diethylstilbestrol-induced vaginal carcinoma following intrauterine exposure.

Another limitation of clinical trials lies in the type of patients enrolled in the studies. In order to simplify the evaluation of drug efficacy and for ethical reasons, patients with complicated disease states, those on multiple drug therapies, the very young and the elderly are frequently excluded from the trials. Clinical trials are never carried out on pregnant women. Consequently, at the time of marketing only limited data is available on any special sensitivities displayed by

TABLE 1

Minimum Cohort Size Required to Detect Various Types of ADRs (7)

Incidence of ADR	Background Incidence	Minimum Number of Patients Required to Detect ADR
1 in 100	0	360
	1 in 10,000	520
	1 in 100	2,000
1 in 1000	0	3,600
	1 in 10,000	7,300
	1 in 100	136,400
1 in 5000	0	18,200
	1 in 10,000	67,400
	1 in 100	3,255,000

several potentially vulnerable populations. Furthermore, little information is provided on drug-drug interactions.

The overall limitations of the premarketing trials have been summed up quite succinctly by Rogers (8), who categorizes them as the "five toos": too few, too brief, too simple, too median aged and too narrow. At the time of marketing only those ADRs, which are relatively common, frequently dose-related, and often related to the pharmacological action of the drug, i.e. type A reactions (9), are known. Type B reactions (9), which are often idiosyncratic or allergic in nature and which occur less frequently, may not have been fully characterized or may be unknown at the time of marketing. For example, the ability of nomifensine to cause a variety of hypersensitivity reactions was known at the time of marketing. However, the potential seriousness of this reaction, which ultimately led to the withdrawal of this product, was not discovered until after marketing (10).

B. POSTMARKETING SURVEILLANCE METHODS

The function of PMS of drugs is to expand upon the data on drug experience collected during premarketing clinical studies. In

particular, PMS aims to identify and quantify the risks associated with drug therapy. In order to function effectively PMS must identify new or unexpected reactions, which may occur only very infrequently and/or after extended treatment with the drug. PMS must provide an estimate of the incidence of ADRs and identify any predisposing factors. Finally, it must possess the ability to rapidly identify serious drug problems and communicate this information in a timely manner so as to minimize the number of individuals who suffer harm from a any such drug.

Perhaps not unexpectedly, all the demands outlined above cannot be met by any one method of PMS. Several different approaches are available and while each has its own unique advantages and limitations, in many cases the weakness of one system is the strength of another. Thus, when operated in concert, the various methods of PMS theoretically possess the capability of providing a sound and thorough system to monitor marketed drugs.

1. Cohort Studies

Cohort studies can be of two types, experimental or observational, depending upon the ability of the investigator to control patients allocation to the different treatment groups.

1a. Experimental Cohort

In experimental cohort studies or clinical trials, participants are randomly allocated to one or more treatment groups, typically, the drug under study vs. control (placebo or alternative treatment) in a double blind or sometimes triple blind (statistician, as well as the patient and physician are unaware of participants treatment) manner.

The elimination of bias associated with the randomization of the treatment groups and through the blinding of the study, make clinical trials the most scientifically pure and the most powerful method of PMS. However, in order to add significantly to premarketing trials, postmarketing clinical trials need to be on a much larger scale and have to have a longer duration than their premarketing counterparts. Thus postmarketing trials or experimental cohort studies require extensive planning to develop and implement, they are time-consuming and extremely

expensive. Additionally, experimental cohort studies have several other draw backs. Firstly, it is not feasible to design these studies to have the capability to detect rare ADRs or those which have a long latency. Secondly, the population recruited for the trials often represents a subset of the total population, which eliminates a number of real life variables. Finally ethical arguments may preclude the use of the placebo group (11).

In summary, despite the scientific elegance of the experimental cohort study, the study of drug use under these artificial conditions is costly and time consuming. Furthermore, these studies are limited in the type of ADR data they provide. They are unable to detect rare ADRs, those that have long latency periods and do not provide the information quickly. Thus, most commonly, postmarketing trials are used to study drug efficacy rather than monitor drug toxicity (12).

1.b. Observational Cohort Studies

Observational cohort studies differ from clinical trials in that the investigator is unable to control the allocation of patients to the different treatment/control groups. Thus a group of patients (cohort) undergoing routine treatment are observed and compared to a second or control group of patients. The control group may be a random sample of the population or a group of patients undergoing some other type of routine treatment. Follow-up of patients may be carried out prospectively or retrospectively by a physician, a review of medical records or through the use of a special registry such as a registry of birth defects. In contrast to some other commonly used methods of PMS such as case-control studies, cohort studies are exploratory i.e. they are able to identify previously unknown problems, and they are also able to quantify the events. On occasions the Food and Drug Administration (FDA) have required drug sponsors to perform postmarketing Phase IV cohort studies in order to supplement the data derived from the premarketing studies.

Though less expensive than experimental trials, observational cohort studies are never-the-less extremely costly. For example, Phase IV studies of cyclobenzaprine and cimetidine were estimated to have cost over $1 million and $5.5 million respectively (13). Thus, it is

impractical to use this method on a routine basis. Furthermore, Rossi et.al (14) investigated the ability of the Phase IV studies of cimetidine, cyclobenzaprine and prazosin to capture new ADRs. The phase IV studies, which had user-cohorts of approximately 10,000, 7,000 and 22,000 respectively, were found to be less effective than the spontaneous reporting system in identifying new ADRs.

2. Case-Control Studies

Case-control studies are retrospective comparison of patients who are identified as having a particular disease (case), compared to a carefully matched control group of the population who do not have the disease. For PMS purposes, the drug history of the two groups are compared to see if exposure to a particular drug is greater among the group experiencing the disease, e.g. a study of estrogen use and endometrial carcinoma (15). Clearly, the selection of appropriate controls is critical to the validity of these studies. For example, a study on the possible relationship between Alzheimer's disease and the use of non-steroidal anti-inflammatory (NSAI) drugs, that did not match the groups with respect to age may falsely identify association between use of these drugs and the incidence of the disease. Alzheimer's disease is more common in the elderly, as is NSAI use. The control group needs to be matched as closely as possible with the case group and should be equally likely to experience drug use.

Case-control studies are widely used and numerous examples can be found in the literature. They can be carried out relatively quickly in comparison to other methods, they can be performed on much smaller groups (16) and they are relatively inexpensive. Additionally, they can be used to investigate the relationship between drug exposure and latent effects, e.g. vaginal carcinoma following intra-uterine exposure to diethylstilbestrol (16).

However, case-control studies are only investigational in nature and cannot be used to identify previously unknown ADRs. They rely on the accurate collection of information, such as previous drug history, which may be subject to recall bias. Most importantly, although they can be performed quickly and inexpensively, the appropriate selection of the cases and controls and, interpretation of the data is critical and

requires a thorough understanding of epidemiological techniques. As a result, case control studies can be subject to much misinterpretation and error and their findings may be very controversial (12).

5. Spontaneous Reporting System

Drug regulatory agencies in most Western countries operate a spontaneous reporting system (SRS) for ADRs. Reports of suspected ADRs are submitted to a central agency, which uses the reports to monitor for unusual patterns of drug-disease associations. In the United States the system is maintained by the FDA (17). Health professionals, primarily physicians, are encouraged to report suspected ADRs on a voluntary basis using the FDA's Drug Experience Report form (1639). A copy form is now found in the Physicians' Desk Reference. The emphasis of the FDA's reporting guidelines is on suspected serious drug reactions, where the event results or contributes to death, is imminently life-threatening, results in or prolongs hospitalization, or results in persistent or significant disability (18). Further emphasis is placed on those suspected serious ADRs that are not be found in the labeling, and those to newly marketed (within the last three years) drugs. Health professionals are reassured that they do not have to establish causality, which is usually impossible to establish from a single case. Thus, each report constitutes only a **suspected** ADR.

In contrast, drug manufacturers are required by law to report to the FDA all domestic reports they receive (19). Manufacturers may receive reports directly from health professionals, from their drug detail representatives or directly from consumers (20). Additionally, manufacturers are required to report certain ADRs received from clinical studies, foreign sources and literature reports. For these latter sources the emphasis is on serious reactions (19).

Approximately 90% of the reports received by the FDA come from manufacturers, originating primarily from physicians and approximately 10% of the FDA reports come directly from health care providers (18), again primarily physicians who constitute the crux of the SRS.

The FDA's computerized data base was established in 1969 and currently contains almost 600,000 reports of suspected ADRs (18). More detailed descriptions of the system can be found in the literature

(17,21). Collectively the data are used to generate signals of potential drug problems, which can then be investigated further, possibly using other methods of PMS. Thus, a primary use of the SRS is as a signal generator. The SRS monitors all drugs used in a variety of real conditions, continuously from the time they are first marketed and it is an extremely cost effective process (22). Owing to this extensive coverage, the SRS is the only method of PMS that is able to detect rare ADRs i.e. those with incidences similar to chloramphenicol-induced aplastic anemia. An efficient system can theoretically identify previously unknown reactions rapidly, particularly when the event is unusual and occurs rapidly after first taking the drug. For example, the U.S. system identified an association between the flank pain syndrome and suprofen use, two-three months after the drug was first marketed in the U.S. (23).

The efficiency of the system is dependent upon physicians ability to detect suspected ADRs (detection), their ability to link the suspected ADR to drug therapy (attribution) and their ability and willingness to report the suspected ADR either to the FDA directly or to the drug manufacturer (reporting). Unfortunately, throughout the world physician participation in such reporting systems is poor. For example a recent study indicated that less than 1% of suspected ADRs classified as serious and/or fatal are reported to the FDA (24,25). A similar study in the United Kingdom estimated that less than 5% of reportable events were actually reported to the Committee on Safety of Medicines (26). Furthermore, Venning found that although physicians provided the first alert to the majority (70%) of what were considered to be the most serious ADRs since thalidomide, in no case was a SRS involved in this first alert (27). However, since the time of Venning's report (1983), spontaneous reports have identified important drug safety problems with nomifensine (10), zomepirac (21), benoxaprofen (21) and suprofen (23).

In addition to under reporting, the SRS suffers several other disadvantages. Reporting is subject to many influences. These include literature reports of ADRs, communications from regulatory agencies and the newness of the drug (23,28,29,30). Additionally, accurate denominator data or data on drug utilization is not available. Finally the reports constitute only suspected events. Thus, clearly SRS data can not be used to reflect the overall occurrence of ADRs nor to calculate

incidence of events. On occasions spontaneous reporting data has been used to provide crude but useful information on the risk-benefit ratios of drugs within the same pharmacological class. For example, the Committee on the Safety of Medicines performed a study on the NSAI, in which they considered the number of reports of suspected serious reactions to drugs in this class, in relationship to the prescription volume for each drug in the United Kingdom (31). In spite of the limitations of SRS data, the study enabled some broad conclusions to be made regarding toxicity profiles of drugs in this class. On another occasion, in the case of flank pain syndrome associated with suprofen use, the SRS provided sufficient data to not only identify but also to resolve a problem of drug safety (23).

In an effort to improve reporting rates in the United States, which traditionally have been lower than the reporting rates in other Western countries (32), the FDA has sponsored state pilot projects to investigate physician under-reporting, and to try to identify and implement various strategies at a local level to increase reporting. Pilot Projects have been established in Rhode Island (24,25,33), Maryland (34,35) Mississippi (36), Massachusetts (37) and Colorado. The Rhode Island (24,25) and Maryland (34) projects conducted surveys to assess physician knowledge, attitudes and behavior regarding reporting ADRs prior to the initiation of interventions. The surveys, which achieved response rates of 75% and 37% respectively obtained similar results. Both found that almost half of their physician respondents were unaware of the FDA's SRS and both identified lack of availability of report forms, lack of certainty the drug caused the reaction and a previous knowledge of the reaction as the major reporting impediments.

The Rhode Island project, which is based in the state Health Department, established a local reporting system in which it assumed an intermediary role between reporting physicians and the FDA. Details of the system are presented elsewhere (33). An educational campaign was mounted to heighten physicians' awareness of the subject, to improve their knowledge of the reporting process and to encourage their participation. After a two year intervention period, physician reporting increased more than 17-fold (33). The increase was accompanied by a corresponding increase in the proportion of serious reports.

Despite a number of short comings, the SRS is a vital component of the PMS process. It is unmatched in the extent of its coverage, its

cost-effectiveness, its ability signal potential drug problems and the speed with which this is accomplished. In this regard the efficiency of the system is compromised only by under reporting, which the FDA-sponsored pilot projects in Rhode Island and other states have demonstrated to be reversible phenomenon. Physicians can be stimulated to report ADRs. Similar increases in the quantity and quality of reporting at the national level would dramatically enhance the efficiency of the SRS to rapidly and efficiently identify drug problems.

4. Data Base Linkage.

The increasing computerization of patients' medical information for administrative and billing purposes has resulted in the creation of large data bases that are potentially useful for PMS. Data base or record linkage refers to the bringing together of two or more individual patient records for a large population. For example, hospital medical records or discharge diagnosis data may be linked to data on drug utilization. Although data base linkage constitutes a specialized data resource rather than a unique type of PMS, the methodology involved in using this data to conduct case-control and cohort studies is relatively new and presents an ongoing challenge to investigators in this field. Several examples of these data bases are presented.

Data from the Group Health Cooperative of Puget Sound, an HMO based in Seattle, has been used by the Boston Collaborative Drug Surveillance Program (38). The system links hospital discharge data and outpatient drug use (38). The HMO has over 300,000 enrollees and has been computerized since 1976. Although the population is rather small the system has been used to investigate a number of issues of drug safety, such as the use of oral contraceptives and the risk of breast cancer (39) and case-control studies on birth defects (40). Other examples of data base linkage systems include the Saskatchewan Health Prescription Drug Plan in Canada and record linkage in Tayside, Scotland. The Saskatchewan plan covers all residents of the province (over 1 million people) and can link prescription drug use to in-patient and out-patient diagnoses (41). The system in Tayside manually identifies patients taking the drug in question, by obtaining photocopies of the prescriptions from the central processing body in Scotland (the

Prescription Pricing Division). This data is then linked using a common community health number to the computerized in-patient hospitalization data (42). Currently the system is restricted to approximately 400,000 but it hopes to expand to include adjacent areas and increase the population covered to over one million.

An additional resource whose application to PMS is being investigated is the billing information routinely collected for Medicaid patients. Medicaid coverage is administered individually by each state and 49 states use a federally certified uniform Medicaid Management Information System (MMIS) to process Medicaid data. A system has been developed, the Computerized On-Line Medicaid Pharmaceutical Analysis System (COMPASS) (43,44), to use Medicaid billing data (including both in-patient and out-patient diagnoses) processed by MMIS for PMS studies. Originally, only data from Michigan and Minnesota were included but since that time an additional eight states have been added to expand the COMPASS population to approximately six million patients. COMPASS may be used to access large cohorts of patients with specific diseases or exposed to particular drugs. Thus both case-control and cohort studies may be performed.

Each of the systems outlined above has its own advantages and limitations. However, in general, the use of existing data bases for PMS purposes offers the advantages of low cost and speed. Additionally, since the populations can be monitored over long periods of time and allow for relatively inexpensive follow-up, they have the potential to detect latent or delayed effects of drugs. Finally, as the data bases increase in size these systems will gain the ability to detect rare adverse events and ADRs associated with infrequently used drugs (45). However, the application of data base linkage to PMS is associated with many inherent and formidable problems, which need to be fully addressed and resolved before data base linkage can become a more prominent method of PMS. These problems include the accuracy, validity and completeness of the prerecorded data and the ability the linkage procedures to operate correctly (44,45). A recent critique (46) of the use of record linkage in PMS concluded that the methodology has not advanced sufficiently to warrant the increased reliance that is being placed on this resource and, furthermore, that the use of information contained on data bases has inherent limitations, which cannot be easily overcome.

These include the ability of the information to provide adequate data on the duration and timing of drug therapy and to adequately define the outcome. The conclusions of this critique were controversial and were subsequently disputed by other researchers in the field (47,48,49,50,51), who claim that many of the problems associated with this resource equally apply to other data resources. Furthermore, it was argued that the ability to rapidly and inexpensively link drug exposure to a medical outcome in a large population, make data base linkage invaluable in its ability to generate signals and investigate issues of drug safety.

5. Prescription Event Monitoring

Prescription event monitoring was developed in the early 1980's by Inman at the Drug Surveillance Research Unit (DSRU) at the University of Southampton and it is a type of specialized cohort study. The Unit uses the Prescription Pricing Authority in Great Britain to identify large cohorts (10-15,000) of patients taking the drug under study. The prescribing physician, who is also identified from the prescription, is then contacted and asked to participate in the study. The physician is provided with a green form and asked to use it to record any serious clinical events that have occurred in the patient during treatment or after when appropriate. A clinical event is defined as, " .. any new diagnosis, any reason for referral to a consultant or admission to hospital (e.g. operation, accident or pregnancy), any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any other complaint which was considered of sufficient importance to enter in the patient's notes." (52). Thus, the physician does not have to suspect the event to be drug related but merely is asked to record any event at all that was considered to be of a sufficiently serious nature to be recorded in the patient's file e.g a broken leg. The green forms are sent out by the DSRH on the anniversary of the individual's first prescription so that all patients are studied for the same period (53). Physician response to PEM has been excellent. It is estimated that 75% of general practitioners in England have participated (52) and that physician response in individual studies has ranged from 55% to 75%.

The DSRH concentrates primarily on newly marketed drugs (1) and a recent study with enalapril for example allowed for the calculation of the frequency of a variety of mild and more serious reactions to this drug (54).

The DSRU is currently evaluating a new reporting scheme, which it introduced in conjunction with the Committee on the Safety of Medicines, in 1987 (53). The function of the new Red Alert system is to promote the timely reporting of serious ADRS to newly marketed drugs. The DSRU identifies the first 20,000 patients to receive a new drug in England and sends the prescribing physicians a special reporting form that bears a distinctive Red Alert triangle. The form is sent out to physicians as soon as possible after the first prescription is written and is personalized for the patient. The physician is asked to use it to report any suspected serious ADRs.

An innovative alternative approach to Inman's PEM has recently been described (55), which made use of what many consider to be an underutilized resource for PMS (56). Bateman and his collegues (55) in the U.K. used community pharmacists to identify a cohort of patients taking metoclopramide and prochlorperazine to study the frequency of extapyramidal side-effects.

In Britain PEM compliments the national spontaneous reporting system (1). In contrast to the SRS, which covers all drugs, PEM is generally only applied to select new drugs. However, PEM can be used to measure incidence and to generate and test hypothesis. Additionally, since events rather than suspected ADRs are captured, PEM may be particularly valuable in identifying new ADRs which are normally difficult to associate with the drug e.g idiosyncratic ADRs. Owing to the size of the cohorts used, PEM cannot detect rare events and owing to the limited follow up period it cannot be used to detect latent effects.

CONCLUSION

The ability of drugs to save lives, prolong lives, improve the quality of life and avoid the necessity of more expensive forms of treatment has had an unquestionable and dramatic effect on the health care system in the latter part of the twentieth century. The sometimes tragic realization that drugs themselves can cause harm also occurred

during this period. Chronologically, events such as the use of diethylene glycol in sulfonamide elixir and the thalidomide disaster lead to the strengthening of the drug approval regulations. Through an increased knowledge of the nature and incidence of ADRs, as well as experience with drugs such as practolol, it became apparent that the assessment of the absolute risks posed by a drug could only be performed by continued and vigilant postmarketing surveillance.

Postmarketing surveillance of drugs is an evolving field, which is still in its development phase. A number of different techniques are available, some of which involve classical epidemiological methodology and some of which, such as the spontaneous reporting system, are unique to drug monitoring. In the near future it is likely that many of the methods discussed in this paper will be expanded, improved and strengthened and that new approaches to the subject will be developed. This may include an expansion of the use and methodology associated with data base linkage, a greater use of pharmacists as a research resource in this field and increase physician participation in the SRS. Continued FDA sponsorship of the state reporting projects could lead to the development of localized areas or sentinels of intensive drug monitoring.

As a final note, it is now clear that drug evaluation is a continuous process that only begins during the premarketing clinical trials. The drug approval process in the United States is frequently criticized for being unnecessarily slow (57) and in consequence that patients are deprived of valuable medications. For example William Wardell estimated that the introduction of beta-blockers has resulted in the saving of approximately 17,000 U.S. lives per year and that by extension the six year delay in the introduction of the beta-blockers in the U.S. cost an unnecessary 100,000 lives. As a result of criticism of this kind, and particularly in response to the demand to expedite the availability of drugs to treat AIDS, the FDA has recently implemented several procedures to facilitate the availability of desperately needed drugs (58). Substantial improvements in the speed and efficiency of the PMS process to capture and quantify ADRs could justify a re-evaluation of the emphasis placed on postmarketing as opposed to premarketing drug monitoring. Thus, the type of accommodations recently made for zidovudine (58), could become more commonplace in the future.

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