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Canada

Drug surveillance system for type B adverse effects: a vision

Vu Xuan Nguyen
Dept. of Epidemiology & Biostatistics
McGill University, Montreal

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Dedication

To: Professor Olli S. Miettinen, my teacher and mentor,
Professor Pierre Robert, my colleague and fellow,
and all my family members.

Preface

Given my professional background in clinical pharmacy, I decided, upon completion of my Pharmacy Doctor program at S.U.N.Y at Buffalo, to pursue the study of principles of applied drug research. To this end, I became in September 1988 a student of the Graduate Diploma Program in Epidemiology & Biostatistics at McGill University, with pharmacoepidemiology as the substantive area of specialization. A few months later, on the advice of Dr Fitzgerald, Pharmacoepidemiology Educational Coordinator, and with the encouragement of Dr Williams, Director of Graduates Studies, I upgraded my registration to the Master of Science Program. In June 1989, I took up my appointment as Assistant Professor of Clinical Pharmacy at the University of Montréal, while keeping my registration in the MSc program.

During my epidemiologic upbringing, I have been fortunate to be able to be exposed to a variety of teachings; and I have learned to appreciate and retain those teachings that seemed to me more intellectually tenable as well as more appealing by their degree of clarity, simplicity and integrity of thought. In these terms, my writing reflects the fact that I have elected to be principally a student of avant-garde epidemiology as it is taught by Professor Olli S. Miettinen.

My efforts to really understand the big picture before narrowing down to my thesis mission have delayed the completion of my thesis work. My progress has also been halted in part by the departure of my thesis supervisors (Dr Fitzgerald and Dr Hill) together with my failure, in 1990-1991, to obtain a positive response to my research grant applications for two potential thesis projects. I continued my study of the principles of pharmacoepidemiologic research, and in 1992, started to devote my efforts to developing, as part of my contribution to the field, a graduate course in pharmacoepidemiology at the University of Montréal. That course focused on principles of pharmacoepidemiologic study design, and I developed and implemented it with the collaboration of my new thesis supervisor, Professor Miettinen. During its implementation in May-June 1994, I learned, from one of the guest speakers, about the development of a Canadian network of regional

centres for the spontaneous reporting of adverse drug reactions (ADRs). Each regional centre would be established within a drug information centre affiliated with a Faculty of pharmacy or medicine, in the framework of a national postmarketing pharmaceutical surveillance program. Given the deployment of such a system, it just seemed to me that its vision would have to be modified if the system is to provide for the scientific risk assessment of type B ADRs.

Against that background, I decided to focus, as for my thesis subject, on that area of outstanding underdevelopment in pharmacoepidemiology: type B risk assessment. With that recent focus, the appropriate research is of the etiologic type. My attendance at the 10th International Conference on Pharmacoepidemiology (August 1994, Stockholm, Sweden), together with my review of the literature, revealed still in 1994 quite a confusion about some of the basic elements related to my thesis work. Many writings about the "case-control" methodology are still flawed, and many studies of drug risks still do not address the types of object that would be directly relevant to drug intervention decisions. As for data resources that are now available for the assessment of drug safety, there is no existing system for the epidemiologic study of type B adverse effects, nor any express vision of what it should be like. Such a vision I set forth here, together with the rationale for it.

The architecture I adopted for this text is a progressive deduction of the vision from the integration of my understanding of three separate topics: the performance desiderata for the surveillance system, the principles of nonexperimental assessment of drug risks, and the nature of type B ADRs themselves and their medical particulars that bear on the design of the system. The emphasis here is to delineate the system's elements that would allow for a rapid quantification of the adverse effect, given a particular hypothesis -- with the quantification being valid and suitably precise. Other important administrative considerations, such as confidentiality, personnel and logistics, organization and finance, etc., are beyond the scope of this text, but I hope that it will stimulate others better fitted than I to initiate appropriate thinking and action.

The important elements that have helped me understand the components of this thesis, and translate that understanding to the vision, besides literature review, were the courses in epidemiologic study design and data analysis taught by Professor Miettinen. I have attended these courses yearly since 1990. I also attended two courses in drug risk assessment, very highly pertinent to this thesis: one at the 1989 McGill Annual Summer Program in Pharmacoepidemiology ("Drug Risks and Programs for their Detection and Quantification" by Miettinen et al.) and one at the 1992 Erasmus Summer Programme in Clinical & Public Health Research Methods ("Drug Risk Assessment" by Miettinen & Grobbee).

Although only about one fifth of the references cited in the bibliography were from Professor Miettinen, much of the theoretical developments retained in this dissertation, especially the concepts and research principles regarding drug risk assessment, are summaries of his writings and teachings. After weighing and consideration, I have heartily adopted these ideas and related terminology, and the reader will find them integrated in my writings, perhaps often even without an explicit quotation. Those avant-garde thinkings are, however, not yet commonly expressed in the epidemiologic literature, and that may make the first reading of the thesis slow and somewhat elaborate. Similarly, although the proposed vision may have been alluded to in the above mentioned courses taught by Pr. Miettinen, its outline and rationale have not yet been elaborated anywhere in the literature.

I cite from the Guidelines for thesis preparation issued by the Faculty of Graduate Studies and Research: "A thesis for the Master's degree must show familiarity with previous work in the field and must demonstrate ability to carry out research and to organize results. The thesis must be expressed in good literate (sic) style. An exhaustive review of work in the particular field is not necessarily required, nor is original scholarship necessarily expected". While the meaning of research was not explained there, I take it to be understood as an activity aiming at the advancement of the current state of knowledge. The concept inherently subsumes theoretical work of this sort.

With this Master's thesis, I submit my modest contribution mainly in the form of a critical review of the status quo of type B risk assessment, a careful selection of the relevant scientific arguments with a diligent highlighting of their eventual contrast with prevailing ideas and concerns, and an organization of the findings aiming at an articulate justification of an original vision that may first appear quite controversial, given the existing approaches to drug safety surveillance.

This work has provided me with a most precious opportunity to be introduced to the beauty of theoretical research, and has helped me grow more comfortable with the topic of meta-experimental drug risk assessment, with special reference to type B adverse reactions. I hope that it would be of interest to the reader as well.

V.X.N.

Acknowledgements

Now looking back at the road I trudged to arrive at this thesis, I wish to acknowledge the academic and financial support I have received from many persons. In 1987, Dr Jacques Gagné, Dean of the Faculty of Pharmacy at the University of Montréal, responded favourably to my request for a one-year, paid, study leave (1988-1989) with a view to developing my research skills in drug epidemiology, before joining his faculty. In September 1988, I was awarded a pharmacoepidemiology fellowship from Dr Walter O. Spitzer, Director of the McGill Collaborative Programme in Pharmacoepidemiology.

In the ensuing years, the main encouragement for sustained scholarly pursuit came from Professor Olli S. Miettinen, who also provided me with precious advice that go very far beyond those commonly given by thesis supervisors. I cannot help but acknowledge his unique commitment and unfailing dedication to the teaching of principles of applied research to his students. I have personally benefited from that commitment, with his providing me countless hours of free consultation for my teaching and research projects in pharmacoepidemiology, always in search of the highest attainable standard of scholarship.

The financial support from the Faculty of Pharmacy and the Fonds C.A.F.I.R. at the University of Montréal and from various pharmaceutical manufacturers, since 1991, has made possible my involvement in many scholarly activities: visits to the pharmacovigilance centres in Paris (France), many research publications, and attendance at several conferences in the area of pharmacoepidemiology.

In September 1992, I was awarded a fellowship from Dr Albert Hofman at Erasmus University and a travelling grant from the Fonds Barré at the University of Montréal, both allowing me to attend a four-week program of intensive study in applied research at the Erasmus Summer Programme, Erasmus University Medical School, Rotterdam, the Netherlands.

In the context of this most immediate thesis work, I am grateful to Professor Miettinen for his suggestion of the thesis subject, his generous sharing of his knowledge and vision about the principles and systems for drug risk assessment, his precious guidance and criticism all along, and his tremendous patience in editing my literary style to make it more accurate and elegant for the English reader, given my primary use of the French language. In the same spirit, I greatly appreciate the thoughtful suggestions made by my colleague, Dr KS Joseph, in the context of his very kind proofreading of my thesis before its initial submission. Finally the constructive comments from both the external examiner, Dr IC Neutel, and the internal examiner, Dr M. Kramer, are also sincerely acknowledged.

For long-term support and encouragement within the University of Montréal, I am indebted to Professor Pierre Robert who has always stood by me during all these challenging times in the development of my academic career.

V.X.N.

Abstract

Since type B adverse drug reactions tend to be rare and serious, they tend to be treated by tertiary-care specialists; and since they are commonly iatrogenic, the specialists should be concerned to document carefully not only the case per se but also the drug use history, leading to practice data of good research quality. The specialists should also be concerned to submit the data record to a central facility that would supply the probabilities, evidence-based, that a recent drug use by a patient caused the adverse event. Continual and systematic accumulation of these data records at the central facility -- using the same logistic and organizational framework for each of different type B events -- provides for both the numerator and denominator series for etiologic research. Since the targeted events are quite rare, the catchment population of the "registry" would have to be very large, international in scope, especially if the system is to provide for rapid resolution of crises arising from novel suspicions of type B effects with respect to newly marketed drugs.

Résumé

Puisque les réactions médicamenteuses indésirables de type B tendent à être rares et sérieuses, elles tendent à être traitées par des spécialistes des soins tertiaires; et puisqu'elles sont généralement iatrogéniques, les spécialistes devraient être soucieux de documenter soigneusement non seulement le cas lui même mais aussi l'histoire d'utilisation médicamenteuse, conduisant à des données de pratique avec une bonne qualité pour la recherche. Les spécialistes devraient aussi être soucieux de soumettre le dossier de données à un établissement central qui fournirait les probabilités, basées sur l'évidence, qu'une récente utilisation médicamenteuse par un patient a causé l'événement indésirable. L'accumulation continue et systématique de ces dossiers de données à l'établissement central -- utilisant le même cadre logistique et organisationnel pour chacun des différents événements de type B -- subvient à la fois à la série du numérateur et à celle du dénominateur pour la recherche étiologique. Puisque les événements ciblés sont assez rares, la population de recrutement du "registre" devrait être très large, d'envergure internationale, surtout si le système doit subvenir à une résolution rapide de crises provenant de nouvelles suspicions d'effets de type B concernant des médicaments nouvellement mis sur le marché.

Contents

1. INTRODUCTION

1.1 Type A vs. type B adverse effects

An adverse effect of a "drug" -- drug use -- is the propensity of the use to produce a particular untoward event or state, an adverse drug reaction (ADR). The risk of a particular ADR -- drug risk -- is the probability that the drug use at issue will produce the ADR. Whereas safety is the antonym of risk, drug safety is nevertheless synonymous with, and a euphemism for, drug risk.

ADRs have been classified into type A (augmented) and type B (bizarre) events/effects. Type A ADRs are the result of an exaggerated but otherwise usual pharmacological action of the drug. Type B ADRs represent aberrant effects that are not the result of the usual pharmacological action of the drug [1].

Type A ADRs tend to be common, dose-related, predictable, and usually not serious. Even if unpredicted, they are primarily discovered before marketing.

Type B effects, by contrast, tend to be rare, not dose-related, unpredictable, and serious, usually with a quite high fatality. They are primarily discovered only after marketing [2 (p. 15)].

Type B reactions, also called idiosyncratic (from Greek "idios", own; "sunkrasis", constitution) reactions, may be allergic in nature, matters of hypersensitivity mediated by the immune system. When non-allergic, many occur as a consequence of genetic aberrations in the production, or intracellular deactivation/detoxification, of toxic metabolites of the drug; by covalent binding to macromolecules, these toxic metabolites lead to an adverse response [3-7].

1.2 Relevance of type B risk assessment

Of the first 18 important adverse reactions to new drugs that were discovered after the thalidomide disaster in 1961, Venning identified 15 as being of type B [8]. Between 1964 and 1987, in the USA and the UK, 29 medications were withdrawn due to safety reasons, with 80% of the withdrawals associated with idiosyncratic ADRs [9,10 (p. 2)]. Another analysis of 79 safety-related drug withdrawals which took place, between 1961 and 1987, in FRG, France, UK, USA and Sweden, revealed that about 70% of them were prompted by concern for type B reactions [10 (p. 72)].

Type B effects also have, up to now, represented the principal focus of epidemiologic studies of adverse drug reactions [11,12], and they are of great concern to the media, politicians, regulatory agencies, and pharmaceutical manufacturers.

1.3 Size requirements for studies of type B adverse effects

Type B adverse events (AEs) usually occur at a general-population rate of less than 1/(10,000 y), i.e., less than one per 10^4 "person-years". Thus agranulocytosis, which occurs as a reaction to a great variety of agents, including drugs, is estimated to have an overall, general-population incidence of the order of 1/(100,000 y) [13]. On the other hand, only half of this rate is suggested by an expensive international (Israel, Spain, West Germany, Italy, Hungary, Bulgaria, Sweden), multi-center, supposedly "population-based" "case-control" study, as it required a period of 4 years for the accrual of a total of 422 cases from a source population of 22 million persons [14].

Addressing toxic epidermal necrolysis, which occurs at a general-population rate of 1-2 cases per 10^6 y, another international "case-control" study [15], is ongoing since 1990 in France, Germany, Italy, and Portugal, with a total source population coverage well in excess of 100 million; it is expected to yield approximately 700 cases by June 1995.

1.4 Existing approaches to type B risk assessment

By the very nature of type B ADRs, suspicions about them arise principally from postmarketing drug experience. Once a hypothesis about a possible type B ADR has arisen (hypothesis generation), the need is formal research aiming at confirmation or refutation of it (hypothesis testing), or at quantification of the drug risk (effect quantification). This means the exploration of whether there indeed is a causal relation between the rate of occurrence of the adverse event and the potential determinant at issue, based on drug use; and, it means the quantification of the occurrence relation at issue [16 (p. 17)]. One may also take the view, however, that there really is not a duality of concerns here, as hypothesis testing is a by-product of effect quantification.

Although 21 types of approach or data resource for the study of drug risk/safety have been described [17-22], these approaches may be classified, in essence, into four categories: phase III ad hoc studies, phase IV published case reports and spontaneous reporting systems, phase IV ad hoc epidemiologic studies/projects, and phase IV surveillance systems/programs. These existing approaches and their limitations with respect to type B risk assessment are reviewed below.

1.4.1 Phase III ad hoc studies

Limitations of phase III studies in respect to type B risk assessment include smallness of the number of patients, typically some 3,000 overall, together with shortness of the duration of follow-up. Notable also is the exclusion of pregnant women, and embryos/fetuses. In order to have even a 50% chance of observing at least one ADR in 3,000 patients, the ADR risk would have to be at least one in 4,300. Thus, type B ADRs generally remain unnoticed in the premarketing phase.

1.4.2 Phase IV published case reports and spontaneous reporting systems

In the postmarketing phase (Phase IV), published case reports and national spontaneous reporting systems (SRSs) have been, to date, the most productive source of new hypotheses about type B ADRs [2 (p. 246),8,10 (p. 21),22]. Both the case reports published in the medical literature and the SRSs have contributed to the production of first reports of possible newly-recognized ADRs [22,23]. Relatively inexpensive and simple, SRSs cover all drugs and a large number of exposed patients, operating from the first day and through the entire duration of a drug's "life". While suspicions of acute (short latency) ADRs can arise from observation in health care practice, SRSs are not prone to generate signals of ADRs which represent much delayed response (long latency) [19,24]. Similarly, suspicions of drug-induced illnesses are not likely to arise from routine practice when the ADRs represent some rather "common" illnesses, or more specifically, when the rate of occurrence of the ADRs is buried in a proportionately high background rate (low rate ratio/etiologic fraction). Moreover, SRSs are quite prone to produce false alarms, as they depend on informal, ad hoc etiologic attribution from the reporters in the context of ignorance about the effect in general. Despite their important role in hypothesis generation, SRSs are totally ineffective for hypothesis testing and effect quantification, due to lack of data on rate denominators.

The US Food and Drug Administration has funded subspecialty registries of suspected ADRs, but despite extensive promotion, they were found not to be an effective or efficient alternative to the general SRS [25]. These ADR registries include the American Academy of Dermatology Adverse Drug Reaction Reporting System, the National Registry of Drug Induced Ocular Side Effects, the Drug Induced Liver Disease Registry, and the Registry for Contrast Media. They are not to be confused, however, with true case registries -- of the epidemiologic surveillance type -- directed to events of selected illnesses regardless of their etiologies.

1.4.3 Phase IV ad hoc epidemiologic studies/projects

Ad hoc epidemiologic studies/projects, different from surveillance programs, have a particular focus/purpose and an a priori limited duration. They can be based on a de novo collection of drug experience data, or alternatively, they can make use of pre-existing data contained within various data resources.

1.4.3.1 Collection of new data

Usually, ad hoc postmarketing experimental trials and "cohort" studies, although adequate for type A ADRs, are insufficient in size for hypothesis generation and especially for hypothesis testing/effect quantification regarding type B ADRs. Indeed, the largest studies involve only tens of thousands of subjects, while millions may be needed. Many strategies of patient enrollment with de novo data collection have been used with these ad hoc cohort studies, including enrollment via the deployment of various networks of health professionals such as general practice physicians, hospital clinical pharmacists, and community pharmacists.

At present, ad hoc "case-control" studies, such as the International Agranulocytosis and Aplastic Anemia Study [14], constitute the only feasible approach to the epidemiologic study of type B effects. These studies are usually concerned with testing a specific advance hypothesis, but they may raise, however, new hypotheses through incidental findings suggestive of other possible drug causes for the particular illness studied. A notable example of this is the retrospective investigation by Herbst et al. who, while searching for factors associated with the unusual occurrence of vaginal adenocarcinoma in a cluster of eight young women, generated and tested the hypothesis of maternal ingestion of stilbestrol during early pregnancy as a cause of tumor appearance years later in the exposed offspring [26].

Ad hoc "case-control" studies have, for one, the drawback of potential for biased recording of exposure information, dependent on the type of medication, the design of

data collection questionnaires, as well as respondent characteristics [15,27] . The long duration of de novo data collection is another important drawback. Despite the logistic and methodological difficulties associated with international case-control studies [28-30], studies of this type seem to be gaining in popularity [15,19], with even a "network of population-based case-control studies" being called for [10 (p. 206)], one based on a proposed "continuous disease surveillance with disease registries providing cases for case-control studies" [31].

1.4.3.2 Use of pre-existing data

Ad hoc epidemiologic projects are also increasingly implemented by investigators who have access to pre-existing data that are available from various resources [19-21]. These data resources may, in essence, be classified into three categories according to the type of database: general mortality/morbidity data, case registry data, and routine-practice data on outcome events and drug uses.

1.4.3.2.1 General mortality/morbidity data

Monitoring of secular changes in cause-specific mortality and morbidity rates may generate ADR signals, especially when accompanied by estimates of drug use. While readily implementable, the utility of such monitoring is, however, quite limited even for hypothesis generation, as the "signal" associated with change in the use of the drug tends to be buried in a proportionately high background rate.

Conceptually, since it involves no individually connected drug use and outcome data, this data resource constitutes a more primitive generator of ADR hypotheses than the spontaneous reporting system. Indeed, it has been used more to help support or refute indirectly a hypothesis generated from other sources [32]. Formal hypothesis testing and effect quantification are not feasible, however.

An example of the utility of this approach is the report by Smith [33] in 1966. Statistics for England and Wales, 1950-1964, showed an increase in asthma mortality among children aged 5-14; and this prompted etiologic investigations. Potential problems due to changes in disease nomenclature or coding of death certificates were ruled out, and an investigation of the circumstances surrounding 184 asthma-attributed deaths suggested a role for pressurized sympathomimetic aerosols. Further studies then correlated the introduction and increasing sales of isoproterenol-containing nebulisers with the increasing asthma death rates, giving additional support to the isoproterenol hypothesis [32]. Case reports suggesting a possible association between overuse of pressurized aerosol bronchodilators and sudden death in patients with asthma [34], however, had already started to appear in 1964.

1.4.3.2.2 Case registry data

Data from case registries are a variant of general mortality/morbidity statistics, with the available advantages of focusing on commonly iatrogenic illnesses of interest and ad hoc recording of drug use. A number of case registries are in operation today, each specific to cases of a particular category of illnesses, such as cancers, birth defects, strokes, severe skin reactions, etc. [2 (p. 188)]. They remain small in size and quite limited in their coverage of the illnesses of interest from the perspective of type B ADRs.

For case registries to be "population-based" (geographically-defined), required is an active attempt to document all cases rigorously diagnosed within a clearly defined region. They can provide estimates of incidence-rates [15,17,21]. Auditing for completeness and accuracy of the data is part of the necessary quality-control program concerning the case ascertainment process of these registries. Completeness is more readily achieved when all possible record sources are being actively reviewed as compared with reliance on reports provided by hospital staff, either spontaneously or through an established reporting system [27].

As with mortality statistics, data from such case registries, that involve no recording of the individual patient drug histories, have served more to shed light on the plausibility of an ADR hypothesis than to generate it. As an illustration, the connection between the introduction of thalidomide and the emergence of the phocomelia epidemic, having been suggested by McBride in 1961, was subsequently supported by review of data from malformation registries: both the appearance and disappearance of the unusual anomaly coincided temporally with the corresponding changes in thalidomide sales, with the appropriate delay of eight months to a year [32].

Highly focused case registries have also been established in response to the confirmation of a new type of drug-induced illness. Thus, a vaginal cancer registry was set up in 1971, consequent to the knowledge of its diethylstilbestrol etiology. The purpose was to provide for the study of the epidemiologic, clinical and pathological aspects of the tumor -- with detailed information obtained on all cases, irrespective of whether there had been any drug exposure [35]. It was pointed out, however, that for epidemiologic purposes the registry had the drawback of involving no "controls" [36].

That approach, also referred to as "case surveillance", has recently been encouraged by a call for the development of a series of registries of commonly iatrogenic, rare conditions/events as a means to ADR hypothesis generation -- with the proviso that they should be based on unbiased case ascertainment and include a routine collection of reliable and full drug histories from patients [10 (p. 186),12, 17-19]. Hypothesis generation would be carried out, presumably, by "regular evaluation of data contained within each registry" [17] or "just by computer examination of frequent associations" [18]; no mention was explicitly made, though, of the denominator series required for hypothesis generation.

As for their use in hypothesis testing/effect quantification, there are many concerns commonly held about case registries. Many of these expressed concerns, however, appear to arise from failure to understand properly the principles of "case surveillance" as applied to a drug surveillance system for type B effects (section 7 below).

1.4.3.2.3 Routine-practice data on outcome events and drug uses

Increased emphasis has been put on the pharmacoepidemiologic deployment of multipurpose, linked/automated databases of routine practice. These are seen to be able to address quickly and relatively inexpensively, and with unbiased data on drug uses, hypotheses that have arisen from other sources and require large "sample sizes" for their testing [37-39]. Examples of these include, in the US, the Group Health Cooperative of Puget Sound, the Kaiser Permanente Medical Care Program, and the Medicaid databases, and, in Canada, the Health Databases in Saskatchewan.

In principle, with these automated databases, cohort or case-control studies could be implemented systematically to screen, and test, for unexpected effects of drug uses, or for drug etiologies of illness outcomes. This is, however, not done routinely in practice [21], and the population sizes are still not sufficient for studies of many type B effects. Other drawbacks of these record-linkage databases, which were originally built-up for administrative/financial purpose, include problems with completeness and accuracy of diagnostic labels, completeness of exposure information, notably for over-the-counter medications, and adequacy of information on covariates [15,27,40].

1.4.4 Phase IV surveillance systems/programs

In 1965, Finney suggested that national and international surveillance, or monitoring, of marketed drugs should be based on the reporting of adverse events (AEs) per se rather than putative ADRs, and that this would have provided for the detection of the thalidomide-phocomelia connection about one and a half years earlier, with the magnitude of the tragedy considerably reduced [41].

In these terms, a drug surveillance system (DSS) -- for "event monitoring" of the Finney type -- is a research program of continual assessment of drug effects, which involves continual and systematic recording of drug uses in addition to AEs, regardless of whether the AEs may be due to a drug; and it involves more or less regular, or routinely repeated,

analyses and reporting of the data, with a view to both hypothesis generation and hypothesis testing/effect quantification.

Contrasting sharply with phase IV SRSs and ad hoc epidemiologic studies, a DSS provides not only for the identification of ADR signals (hypothesis generation) but also for verification of reported signals/suspicions of ADRs (hypothesis testing), as well as quantification of the risk of known adverse effects by formal epidemiologic analyses [24,42,43]. In that respect, one may think of the DSSs as actual, multipurpose research systems, as contrasted with SRSs that are non-research multipurpose systems. Contrasting with the multipurpose, automated databases of routine practice, the DSSs while being also integrated with routine clinical practice, are originally and primarily designed to collect data on outcome events and drug uses for the purpose of scientific -- not administrative -- research, especially with a view to actually carry out regular assessment of drug effects.

DSSs may be classified according to who recorded the original/primary data, before submitting the data records to the DSS central facility for data processing. In that respect, the data records may be completed by specially trained research monitors who extract data from the clinical records and interview the patients and their attending physicians, as it is done in the US with the Boston Collaborative Drug Surveillance Program (BCDSP) [42] and with the Case Control Surveillance program (CCS) [44]. Alternatively, the data records may be completed by the medical practitioners themselves who are actually taking care of the individual patients, as it is done in the UK with the Prescription Event Monitoring program (PEM) [45] and with the VAMP multipurpose research database [18,46].

Some of these DSSs have involved follow-up of cohorts -- closed populations -- that are formed within a hospital setting, as with the BCDSP initiated in 1965, or that are formed in an outpatient setting, as with the PEM program initiated in 1981 and the VAMP system initiated in 1985. Representing an alternative strategy, the CCS program was introduced by the Drug Epidemiology Unit in 1976 (now the Slone Epidemiology Unit) [47], and involved follow-up of catchment populations, generally dynamic/open. Its purpose is

systematic hypothesis generation and hypothesis testing about drug-induced illnesses by the use of an ongoing in-hospital accrual of data on a wide range of targeted illnesses (about 50) and on all drug uses, and regular screening of the database with the case-control approach to explore illness-drug associations.

The role of these existing multipurpose research systems with respect to type B ADRs remains, however, limited on account of the limited size of their population coverage, with the current largest one, the VAMP system, covering about four million patients.

1.5 Overview of the status quo of type B risk assessment

Reviewed above were the existing approaches available for the epidemiologic assessment of drug risks/safety, with special reference to type B risk assessment. By their rare and undelayed nature, suspicions about type B ADRs arise informally in actual practice. These suspicions come to public attention via phase IV published case reports and spontaneous reporting systems. Formal, scientific evidence is, however, required for informed decision-making, but such evidence is often not available at the time of the regulatory crisis. Because of this, and since decisions of "not to act" are harder to explain to the public and media, drugs are frequently withdrawn or banned, or their market is severely restricted, under considerable ignorance about the hypothesized adverse effect [48-50] -- with hundreds of millions of dollars of investment as well as an effective and also possibly safe drug lost almost overnight.

Phase IV ad hoc "case-control" studies constitute, at present, the only feasible approach to the epidemiologic study of type B effects with, however, an important drawback, that is a long delay due to their ad hoc, de novo data collection, cost considerations besides. Great hope has been invested in multipurpose record-linkage databases with routine pre-existing data available for a swift resolution of the regulatory crises that the suspicions bring about [51,52]; but their sizes, even, remain wanting for sufficiently precise assessments of type B effects, especially for newly marketed drugs. Other important drawbacks of these automated databases include problems with completeness and accuracy

of diagnostic labels, completeness of drug use histories, and adequacy of information on covariates.

Existing Phase IV surveillance systems/programs play only a very limited role with respect to type B effects, since they are concerned only with a limited segment of drug experience. In that respect, failure to distinguish between the type A and type B ADRs is manifest even in a recent blueprint for the development of a national postmarketing pharmaceutical surveillance program in Canada [53].

Continuous monitoring of rare and serious illnesses for changes in incidence, coupled with ad hoc case-control/case-referent studies, has been suggested since the late 70's [24,54]. In these terms, suggestion of regular surveillance, with ongoing case-controlling of selected rare illnesses frequently associated with drugs, was reiterated by Shapiro in the late 80's, to "discover and quantify associations between these diseases and drug use in general" [55]. Shapiro recently stated, however, that "case-control surveillance cannot monitor exceedingly rare diseases, but the possibility that the methods can be suitably modified in order to do so is being explored" [44].

Along the same line, Carson and colleagues [22,56] suggested that:

> An alternative and complementary approach to screen for unknown drug effects is to perform a series of case-control studies ... Cases would be defined as diseases which are commonly caused by drugs ... Four controls per case would be randomly chosen from the remaining population and antecedent drug exposures would be compared. Each case-control study would be repeated at regular intervals ... However, since such hypotheses arose from the same data and were not a priori hypotheses, these analyses cannot be considered as testing hypotheses and further corroboration would be required from other data.

In summary, risk assessment with respect to type B adverse effects is still wanting, as there remains a dramatic lack of pre-existing systems of data available for immediate analysis at the time that the suspicion arises, with unwarranted bannings or withdrawals

of drugs the consequence of this. On the other hand, many other type B effects of public health importance may still go unrecognized or are discovered only with much delay. There thus remains a need to find a solution.

2. PRESENT WORK

Given the status quo of type B risk assessment, the beginning of the solution is a tenable vision as to what type of system should exist for the postmarketing surveillance of type B effects. Should the vision get to be accepted, the next mission would be to seek to see to it that such a vision is implemented.

2.1 Objective

The objective of the present work is to arrive at an intellectually tenable vision of a drug surveillance system for the epidemiologic study of type B adverse effects.

2.2 Approach

The vision I set forth here is deduced from the integration of my understanding of three separate topics, on account of the following set of principles.

One should not begin to design any system of surveillance or have any vision about it without knowing the performance desiderata for such a system. Therefore, understanding of what are the performance desiderata for a drug surveillance system (DSS) for type B effects, drawing from the status quo and the limitations of existing approaches to type B risk assessment, is essential for rational design of the system, as well as for its evaluation upon implementation.

Since the system is expected to be a research system, a scientific resource capable of yielding formal evidence on drug risks that is required for informed decision-making, its rational design also requires a thorough understanding of the principles of epidemiologic

-- occurrence -- research that pertain to the topic of drug risk assessment, with special reference to type B ADRs.

Finally, the nature of a given DSS will depend inherently on the nature of the adverse events (AEs) it is supposed to monitor. For example, the vision of a DSS for type B effects will be different from that of a DSS for type A ADRs. It is thus pertinent to understand, in the light of the research principles on type B risk assessment, what is the general nature of type B ADRs themselves and how their medical particulars would bear on the system's design.

Chapters 3 to 5 delineate these aspects of the three points of departure, meaning, the performance desiderata for a type B DSS, the principles of nonexperimental drug risk assessment, and the system implications of the medical particulars of the type B AEs. By type B AEs, throughout this text, I mean the adverse events of concern in respect to type B ADRs. Then, flowing from these considerations, chapter 6 delineates, as an immediate corollary, the system's vision in broadest outline; the particulars and some general features of the system are also presented. In chapter 7, before the conclusion, I discuss some prevailing concerns that pertain to the topic of "case surveillance" related to the system's design, and some future work that would need to be carried out.

3. DRUG SURVEILLANCE SYSTEM : PERFORMANCE DESIDERATA

A DSS for type B adverse effects should allow for the identification of early signals of previously unsuspected type B effects, as well as a rapid quantification of the effect/risk, whenever a particular suspicion/hypothesis arises either from within or outside of the system. A rapid output from the DSS is not, however, an end in itself. Rapidity of the system's output is a desideratum that needs to be linked with the nature of the output itself, meaning, the quantification must also be valid and sufficiently precise.

In other words, the DSS should quickly dispose of a large proportion of the alarms arising from non-research generators of hypotheses such as the spontaneous reports, allowing for

swift regulatory decisions, say within weeks, to be made on the basis of scientific quantification of the alleged adverse effect; that is, in the light not of ignorance but good research-based assessment of the suspected effect.

There are other system desiderata that are not of the performance type. They include, for example, issues of confidentiality, protection of industry competitive secrets, and contribution to public policy, clinical etiognosis and scientific publication. These desiderata, as well as the system's personnel, logistic, financial and organizational aspects, represent important considerations that are beyond the scope of this thesis.

4. PRINCIPLES OF DRUG RISK ASSESSMENT

Effect is the change in an outcome occurrence produced by a particular category, relative to another category, of a determinant [16 (p. 325)]. In studying the effects of drug interventions, three basic study designs are available for the investigator to choose from: experimental, quasi-experimental ("cohort"), and meta-experimental ("case-control") [57]. Moreover, given the extremely uncommon occurrence of type B AEs, for an efficient quantification of type B adverse effects, the only conceivable approach is the meta-experimental type of study. The principles of such studies have been delineated [16,57-64] by Miettinen, whose thinkings may differ, however, from those of many other authors who refer, still, to the traditional "case-control" methodologic approach [65-69].

4.1 Relevant objects in drug risk assessment

The concept of risk is related to that of incidence proportion. Risk, in a given individual, is the probability that an untoward event will occur [70]. For an individual of a given type, the risk of an AE over a given risk period is the expected, theoretical, cumulative incidence rate of the event over the same period of time for people of the type at issue. That expected rate results from the expected incidence densities specific for the component periods involved, an incidence density being the ratio of the number of events to the corresponding population-time of follow-up [16 (p. 249),61]. It should be noted

that risk is inherently a theoretical, non-empirical entity, whereas a rate of occurrence -- in a population experience -- can be either theoretical or empirical.

Risk assessment can be a matter of descriptively relating the incidence of an AE to subject characteristics -- determinants of incidence, risk indicators -- jointly, without any view to causal interpretation of the relation. On the other hand, causal interpretation of the occurrence relation, with extraneous explanations eliminated, is essentially required for rational intervention decision and for etiologic insight [16 (p. 11)]. In the study of AEs commonly drug-induced, extraneous explanations -- potential confounders -- are notably ones having to do with exposures to other etiologic drugs.

Drug intervention decisions depend on knowledge about the risks of particular adverse reactions to the potential drug use, given the contemplated/intended type of use in the type of potential user. The type of drug use is defined as to the drug product (not the molecule) and the route, dosage, and duration of its use. The type of user is characterized according to the modifiers of effects of drug use. Thus, for type A and type B ADRs, risk has to be defined per duration of use, and components of the risk period are to be viewed in terms of the potential duration of use and the wash-out period [61,62]. For type B effect in the context of first use, when one looks at the occurrence of the AE on the scientific, cohort/drug-intervention time scale, the incidence/risk density is inconstant in time, with an initial increase followed by a decrease (Appendix 9.1 - Figure). In repeat/subsequent uses, risk is lower, due to selection against the susceptibles who already have experienced the AE with previous uses. The duration of previous use is thus an important modifier of drug risk, for both type A and type B ADRs, such that the longer the duration of previous drug use with no AE, the lower the risk associated with current/recent use.

Therefore, risk of an ADR over the total risk period will depend on -- and is to be studied in terms of -- incidence density differences specific to the various subintervals of duration of the risk period, that is, specific for various time intervals subsequent to the initiation of drug use, conditionally on modifiers and confounders [61]. This contrasts rather

sharply with other types of object that are reported in many epidemiologic studies about drug risk, such as the number of cases per 10^6 defined daily doses [71,84], or the relative risk, or the odds ratio [72,75]. To me, these latter study objects do not provide the potential user with sufficient quantitative knowledge about the risk he/she is about to take when selection is carried out at the drug intervention decision node.

As for clinical etiognosis, that is, the setting of a probability of causation of a particular instance of an AE by a potential etiologic exposure, the requisite knowledge has to do with the proportion of instances of the AE in which it is caused by the drug "exposure", given the particular history of drug use/exposure and the type of user at issue, who is also characterized by a particular modifier profile as for the effect of this exposure. That proportion -- the etiologic fraction (EF) -- represents the etiognostic probability (P) for that drug use in users like that [57], and it is implied by the causal incidence-density ratio (IDR) specific to the history and the modifier profile: $P = EF = (IDR-1)/IDR$.

4.2 Traditional "case-control" methodology

In the context of traditional epidemiologic teaching [65-69], "observational" methods include case analysis, cases series analysis, secular trend analysis, cross-sectional studies, cohort studies, and case-control studies. While cohort and case-control studies are the two major observational designs used in pharmacoepidemiology, the case-control approach is the method of choice for studying a rare "disease" and multiple etiologies. "Relative risk" is the key statistic reported from theses studies: it is the ratio of the incidence rate of an outcome in the exposed group to that in the unexposed group [68].

Case-control studies proceed in the opposite "direction" from "follow-up" studies, beginning with the identification of cases of the disease of interest and a "control" group of subjects without the disease, and retrospectively determining the exposure status, looking for "differences in antecedent exposures" between the two "groups" [15,68,69]. The selection of the controls is based largely on the skills and expertise of the researcher [66].

Because the population "at risk" of developing the AE is not known in a case-control study, it is not possible to compute directly the incidence rates, hence, the relative risk. As a substitute, one generally reports the "odds ratio", which is an estimate of the relative risk when the disease under study is relatively "rare" [67-69]. That disadvantage can be overcome with a "population-based" study, in which all cases in a defined population are enrolled, and the overall incidence as well as absolute and relative risks can be estimated [15].

The case-control study is, however, particularly prone to a number of biases, notably selection bias and recall bias [67,69]. Critical considerations are identifying cases and controls that are "comparable" for "all variables" that may confound the study outcome, and assuring that cases and controls arise from the same defined population, even though that population's nature may not be clearly known [66].

Many of these prevailing ideas about drug-epidemiologic research from the traditional "case-control" point of view contrast with those from the meta-experimental outlook described in the sections below. From this latter outlook, one may learn, for example, that matching the "controls" to the "cases" does not prevent confounding, and that the so-called "odds ratio" is in fact, conceptually, an incidence-density ratio with no need for "rare disease assumption" (Appendix 9.2 - Table).

The latter outlook is the one that I have adopted for my study of the principles of research pertaining to the assessment of type B effects.

4.3 Meta-experimental means of drug risk assessment: its essence

In any study of incidence/risk, inherently including documentation of empirical incidence, follow-up of a population over time is inescapable. There are essentially only two types of population, either a cohort or a dynamic population. A cohort is a population with fixed membership; such a population membership is defined on the basis of some event, for ever thereafter. A dynamic population is a population with turnover of membership;

such a population membership is defined on the basis of some state, for the duration of that state. A "cross-sectional" population is a misnomer for a population cross-section, that is, the status of a population (cohort or dynamic) as of a particular point in calendar time or in the individual's time.

Whereas the study population in experiments and quasi-experiments is inherently a cohort (open population), in a meta-experimental study, it is inherently dynamic (open) rather than a cohort. Therefore, it can only be defined, rather than operationally formed, within the study's source population. The membership at any given moment is a matter of meeting at that moment the criteria defining the membership state, the study population's membership criteria. Principal among these are: 1) representation (at that moment) of the study domain, such as the criterion of candidacy for the AE, with preferably no AE during previous drug use, and other pertinent restrictions as well; and 2) representation (at that moment) of one of the contrasted categories of history of recent use of the drug under study.

The concern is to document the rate -- incidence density -- of occurrence of the AE in causal relation to recent histories of the drug's use over the entire span of retrospective, etiologic time, in the context of type B AEs a matter of hours or days only. These histories of drug exposure define patterns of intensity of use over the entire span of etiologic time antecedent to T_0, the time of outcome occurrence, including the pattern of no "exposure" at any time within that period. That specific span of time under investigation, the etiologic period, is the period of time antecedent to the outcome where the etiologic experience explanatory of the AE could have taken place. In the context of type B AEs, it is the immediate period of recent drug uses from the outcome backward.

Thus, in broadest terms, the source population -- dynamic or cohort -- consists of two dynamic subpopulations: an extraneous population and the study population; and in simplest terms, the latter is composed of the index population of "recent" users and the reference population of "recent" nonusers of the drug at issue. The latter, reference

population may be defined as recent users of an alternative drug known not to cause the AE ("placebo" exposure).

Operationally, the source population, with the study population embedded within, is followed over the calendar-time period of case accrual, providing for the source population-time or source base. The source population follow-up yields a first-stage numerator series of cases of the AE identified from the "registry", and the source base is sampled for a first-stage denominator series. Both series are then restricted, by use of the study population's membership criteria, to the events/person-moments actually representing the study population-time or study base. Upon this restriction, the case series provides numerators of the rates being documented; the denominator series provides numbers stochastically proportional to the actual, population-time, denominators -- numbers referred to as quasi-denominators in this sense (Appendix 9.2 - Table).

For various time intervals subsequent to the initiation of the drug use, the numerators coupled with the quasi-denominators provide for comparison of quasi-rates corresponding to the various histories of the drug's use, conditional on confounders and modifiers (section 4.5 below). Difference in the quasi-rates is translatable to actual incidence density difference and to risk difference -- excess risk -- for each time interval. Then, for each contemplated duration of use in the particular type of potential user, the total ADR risk is approximately equal to the sum of the risk differences over the intervals during and after the contemplated use of the drug (Appendix 9.1 - Figure).

Operationally, the source population for the first-stage numerator series may have a primary definition, with the case ascertainment scheme having no role in its definition; that is, the primary commitment may be made to a particular source population, either cohort or dynamic, which is enumerable at any given moment. Coupled with this commitment to a primary-defined denominator is the necessity to obtain a corresponding complete first-stage numerator series -- census of cases -- or, at least, a determinant-representative subset of the cases occurring during the source-population follow-up.

Alternatively, and especially in the context of very rare AEs, like type B AEs, the source population may have a secondary definition, with primary definition given to the means of obtaining the first-stage numerator series, its identification from a particular case registry; that is, the primary commitment is made to a particular scheme of obtaining the first-stage case series, which is always a census of cases by definition. Inherent in this primary commitment is the definition, secondary, of the corresponding source population for the first-stage numerator series, such that: at any given moment, it consists of all people with the "were-would" property that were a case of the AE to occur, it would be "caught" by the particular case ascertainment scheme, the "registry". That secondary source population is the "catchment population", dynamic, of the particular case ascertainment scheme, or in other words, the registry's catchment population for the AE at issue.

Were a particular case ascertainment scheme to be such that the first-stage numerator series is overloaded with index/"exposed" cases, its corresponding catchment population would also be, by definition, similarly over-represented with the index category of the determinant, as this is inherent in the "were-would" property. In principle, a successful determinant-representative sampling of that overloaded catchment population's follow-up would still provide for a valid first-stage denominator series, although such a sampling would tend to be infeasible in practice. As a consequence, coupled with the use of a secondary source base is the necessity to define the AE in such a way that the drug use history plays no role in its case ascertainment process, and thereby no role in the "were-would" property of the catchment population for the AE at issue, thus providing for the feasibility of a determinant-representative sampling of the secondary source base.

For example, a situation in which the case ascertainment scheme may be overloaded with index cases occurs when the patient referral to the hospital depends directly on knowledge of the subject's drug use history subsequent to awareness of the ADR hypothesis. The same occurs when the likelihood of hospitalization for the illness outcome under study, that is, the detectability of the illness, depends on the subject's degree of "medicalization", since "medicalization" is quite usually associated with the propensity to use drugs.

4.4 Meta-experiment: validity requirements and assurance

4.4.1 Validity requirements

Four requirements of validity for meta-experimental research on ADRs [16,57-61] are to be satisfied: 1) completeness of outcome documentation, or at least its equi-accuracy -- equal degree of freedom from error -- between the contrasted categories of the determinant; that is, a passive case accrual or an active case ascertainment process independent of the history of drug use; 2) representative sampling of the source base for the first-stage denominator series -- representative as for the distribution of the drug use history, either within the source base at large or within each of the confounder/modifier strata accounted for in the analysis; 3) completeness of documentation of drug use history, or at least its equi-accuracy between the numerator and denominator series; that is, drug use record abstraction, interview process, and patient recall independent of the outcome status (case, noncase); and 4) absence, or thorough control, of potential confounding; that is, absence or control of differences between the index and reference subpopulations in terms of extraneous determinants of the AE risk, notably with respect to contraindications and exposures to other etiologic drugs.

Potential selection bias in a meta-experimental study is a matter of retrospective commitment to a source population on the basis of some information about the occurrence relation in it. Selection bias also occurs when sampling for the first-stage denominator series was not representative as for the distribution of the drug use history.

There are some subject characteristics, rather difficult to measure, that may confound the study of drug etiologies of illness, notably the severity of the indication, the severity of the contraindication, and the degree of "medicalization". An indication for a particular drug use is a user's characteristic -- such as a condition, a circumstance, a behaviour -- that calls for considerations of use, or that prompted the drug use. A contraindication for a particular drug use is a user's characteristic that indicates a perceived high risk for a given AE that the drug use may promote, and, consequently, indicates prohibition of the

drug use [73]. In the study of adverse effects, confounding by indication is in general a nonissue, since the indication is not generally a determinant of the occurrence of the AE. Analogously with confounding by indication in the study of an intended effect, confounding by contraindications, in the study of adverse effects, tends to reduce, or even reverse, the empirical relation. The magnitude of the problem is, however, quite different, since an indication is quite regularly present in studies on efficacy whereas any given contraindication is present only occasionally in studies on toxicity [58]. Whereas confounding by contraindications may be an issue in the study of type A adverse effects, in type B drug risk assessment, contraindications by contrast are uncommon in themselves and rarely have to do with the risk of type B AEs. By contrast to type A ADRs, a history of previous occurrence of the AE in association with the exposure constitutes an absolute contraindication to further exposure.

The growing "medicalization of life" has been described by Illich, in 1975, as "a by-product of an over-industrialized society and the expropriation of health by the medical establishment", as well as , among other features, "the dependence on professional care and the addiction to medical drugs" [83]. In other words, the "medicalization" of a subject is a subject's characteristic that indicates his propensity to use health care. "Confounding by medicalization" is thus a general issue in the study of the drug etiology of illnesses, since medicalization is a close correlate of other etiologic drug uses.

4.4.2 Validity assurance

4.4.2.1 Outcome documentation

With a primary source base, completeness -- or at least equi-accuracy -- of the case ascertainment process, which depends on the completeness of case hospitalization, case diagnosis, and case registration, is assured by the following means: 1) a focus on severe cases; 2) a mandatory diagnostic protocol that includes standardized AE definition and diagnostic procedures; 3) a mandatory reporting scheme to the central "registry"; and, 4) auditing procedures.

Diagnostic auditing that targets all possible sources of potential cases, with observer blinding when feasible, will help to assure the completeness of case diagnosis, i.e., decrease the number of missed cases; on the other hand, auditing the records of cases already diagnosed by routine health-care practice will increase the accuracy of case diagnosis, i.e., decrease the number of false positive results. Auditing the logs of all possible sources of records of diagnosed cases will assure the completeness of case reporting to the central registry. Finally, a swift analysis of the data already collected when the first suspicion arises and before awareness of the ADR hypothesis spreads will also enhance equi-accuracy of the case ascertainment process.

With a secondary source base, all cases are documented/registered, by definition, but the process that brings cases to the registry still needs to be independent of the drug exposure status to provide for feasibility of a determinant-representative sampling for the denominator series. The same assurance means as above still apply.

4.4.2.2 Source-base sampling

Selecting a primary source base is the preferred option for its valid sampling, since this implies the availability of a sampling frame from an enumerable source population, such as the population of a prepaid health plan, a "study cohort", or a metropolitan population. It is then either a matter of simple sampling of the source base at large, or a matter of stratified sampling within the confounder/modifier strata that are accounted for in the analysis.

With a secondary source base, as deployed in the study of type B effects, valid sampling, that is a determinant-representative sampling of the registry's catchment population for the studied AE, is achieved by selecting cases of an extraneous AE from the same registry, such that: 1) the extraneous AE shares the catchment population with the studied AE, that is, they are similar as to the relevant factors that bear on their ultimate appearance in the registry; and, 2) the occurrence of the extraneous AE is independent of the drug exposure under study. Both of these requirements are matters of judgement.

Assurance of valid sampling of the secondary source base is enhanced by selecting three or four extraneous AEs to help verify validity of the sampling. Assurance of shared catchment population is also enhanced by the operational means that would lead to an "obligatory registration" of the cases -- with essentially complete capture of cases of the extraneous and the studied AEs by the same registry. These means are notably: 1) focus on severe cases of the extraneous and the studied AEs so that all of these cases get to be hospitalized; and, 2) coverage of all registries -- hospitals/facilities -- within a geographically defined, metropolitan, area with admissible cases restricted to the local residents.

It should be noted that, when the two operational means mentioned above can be implemented, the difference between the conceptual, not enumerable, catchment population for the AE at issue and the primary, enumerable, source population for the AE at issue, like a metropolitan population, tends to disappear. Indeed, when the first condition is met, the various case ascertainment schemes would be independent of the degree of medicalization of the subject or of knowledge of the subject's drug use history, and their corresponding catchment populations would have an accurate representation of the drug use histories, that is a representation not overloaded with index users. These various catchment populations could still have, however, a different geographic coverage, and consequently, their respective distributions of the drug use history could still not yet coincide. This occurs for example, if the various AEs, even from the same registry, differ in some registration factors, such as differential reputations for various AE-related medical specialties. When the second condition is also met, the various catchment populations would converge towards a same one with a same drug use distribution as for that of the source base for the studied AE.

4.4.2.3 Documentation of drug use history

With drug use record abstraction, the use of records of drug exposure before the outcome (case, noncase) provides for a documentation of drug use histories independently of the

outcome status. Equi-accuracy of record abstraction is enhanced by standardized abstraction protocol and blinding of the abstractor as to outcome status.

With patient interview/recall, equi-accuracy of drug use histories is enhanced by designing: 1) identical structures of interview, including blinding of the interviewer as to the outcome status and blinding of both interviewer and patient as to the ADR hypothesis at issue; and 2) identical settings of interview are similar as to the milieu, the interviewer, the mental condition and the socio-cultural characteristics of the subjects. Assurance of equi-accuracy of drug use histories is also enhanced by proper selection of the extraneous AE such that: 1) they have an equal sudden/rapid onset, thus allowing for an equal accuracy in the operational definition of T_o, the time of outcome occurrence, necessary for the taking of time-accurate drug use histories; and, 2) the concerns for the histories are equal between the persons involved in the numerator and denominator series.

4.4.2.4 Potential confounding

With respect to uncontrollable ("soft") confounders, the preferred means of validity assurance for potential confounding is to accent its prevention, notably by selecting an appropriate population and/or treatment contrast such that the potential confounders are equally associated with each category of the population/determinant contrast(s). Thus, contrasting a potential etiologic drug use with an alternative drug use that is known not to cause the AE ("placebo" exposure) and known to be equally deployed for the same indication would prevent any potential confounding by indication.

With respect to controllable ("hard") confounders, a complete identification and accurate documentation of the potential confounders for thorough control in the analysis is necessary.

Matching of the denominator to the numerator series, according to potential confounders, plays no role in the prevention of confounding. This type 2 matching, as contrasted with the type 1 matching of the "unexposed" to the "exposed" subjects, is a matter of stratified

sampling of the source base. It is important to note that confounding resides in the actual denominator, the source base, not in the denominator series. Were a source base to be confounded, no matter how carefully we "match" -- sample that source base, the source population-time is and remains confounded, as well as for the study base imbedded within. In that sense, the investigator will still have to do a stratified analysis, controlling for differential distributions of the confounders between the index and reference subpopulations in the study base.

4.5 Meta-experimental study of drug risk: data reduction

Drug risk over the total risk period is studied by focusing on the excess incidence densities/incidence density differences (IDDs) specific to various subintervals of the risk period, conditionally on confounders and modifiers. To provide for the computation of these various incidence densities (IDs), subjects from the index population are classified first according to the category of duration of attained exposure, that is, the time-interval since initiation, and further, within it, according to category of duration of recent discontinuation, that is, the time-interval since discontinuation [61]. This classification scheme, which refers to various index subpopulations, defines the specific index subcategories of "recent exposure" to drug, to be contrasted with the reference category of no "exposure" at any time within the risk period.

For each subinterval of duration in the risk period, as defined by the specific subcategory of recent exposure in which the index subjects were classified, the numerators coupled with the quasi-denominators provide for comparison of quasi-rates. The difference between index and reference quasi-rates, the quasi-rate difference, is translatable to actual incidence density difference (idd), given a "population-based" study. Summarizing that empirical idd over the confounder strata, within a modifier stratum, yields an overall empirical value of idd (idd*) [64] (Appendix 9.2 - Table). That datum idd* is the frequentist "point estimate" of the theoretical IDD, presumed constant over the confounder strata.

Having derived a descriptive statistic, the empirical value idd*, for the effect measure of interest (IDD), data analysis proper involves the invocation of a series of statistical models that define the sampling distribution of the datum idd* for each possible value IDD_i of the theoretical quantity IDD. That provides for the derivation of inferential statistics serving as a basis of inference about the theoretical object IDD.

4.6 Type B risk assessment: type and size of source population

Given the uncommon occurrence of type B AEs, the only conceivable epidemiologic approach for their study is the meta-experiment. Operationally, in a meta-experimental study, two fundamental options for the type of source population are available for the investigator to choose from: either a primary definition of a particular source population (cohort or dynamic) which is enumerable at any given moment, or alternatively, a secondary definition of a corresponding source population (dynamic) of a particular case ascertainment scheme, the non-enumerable catchment population of the registry for the particular AE at issue.

The commitment to a primary source population, although generally the preferred option, requires that two conditions be met: all the cases, as defined (by severity, i.a.), are hospitalized, and, coverage of all institutions in a geographically defined area can be secured. This second condition may not be readily achievable in the context of a drug surveillance program with no regulatory requirement for mandatory reporting of the outcome events. In that context where one has to rely on the good will and long lasting ccoperation of the participating facilities/practitioners to report consistently all cases of the AEs of concern, one can only realistically expect to count on the effective cooperation of some select hospitals, and hence, one needs to invoke the follow-up of a conceptual population -- the catchment population of these select hospital registries for the AEs of concern. Therefore, a secondary source population is the only option to entertain seriously in the context of a program of surveillance of unlimited duration.

Given the concern for very rare AEs occurring at a rate of one case per 10^5 person-years or less in the catchment population, needed is a large population experience to provide for sufficient precision in quantification of excess risk in terms of IDD. Theoretical considerations (Appendix 9.3) suggest a size of 100 million persons or more for the secondary source population, thus, the catchment population of the DSS registry for the AEs of concern being international in scope. An even larger catchment population would be required if the DSS is expected to cover a large proportion of the populations exposed to newly marketed drugs.

5. SYSTEM IMPLICATIONS OF MEDICAL PARTICULARS

In the context of a surveillance system, rather than an ad hoc research project, and in the light of the above principles of meta-experimental research, let us now contemplate the general nature of type B ADRs and how their medical particulars would bear on the system's design.

5.1 Accessibility of numerator events (cases)

5.1.1 Specialized tertiary care

Since type B AEs tend to be rare and serious, they tend to be treated by tertiary-care specialists in a given subspecialty, such as haematology, hepatology, dermatology, and others. This means that contacting only the few specialists in a given subspecialty will allow for the capture of all cases of type B events that come from a very large catchment/candidate population and relate to that subspecialty.

5.1.2 Limited number of relevant subspecialties

In an analysis of 29 ADR-related drug discontinuations from the US and the UK markets from 1964 to 1987, Lanctôt et al. found that "only six categories of idiosyncratic ADRs

were associated with 80% of the drugs withdrawn: hepatotoxicity, hypersensitivity, nephrotoxicity, carcinogenicity, hematological reactions, and neurotoxicity" [9,10(p. 2)].

Between 1961 and 1987, Spriet-Pourra & Auriche identified in four countries 77 cases of product withdrawal for reasons related to safety, with the usual reasons being ADRs observed in man (66 cases). Most of these adverse effects were type B ADRs, with the most frequent effects being hepatic (14/66), haematological (12/66), and neurological (9/66). These three categories accounted for 50% of the ADR-related withdrawals [74], out of a total number of 10 different, "organ-specific" categories of type B effects that were associated with all these drug withdrawals (Appendix 9.4).

Thus, only a very limited number of subspecialties are relevant, and again, the interface with only a limited number of tertiary-care specialists will allow for a large coverage of the aggregate number of type B events, meaning an unusual and fortunate accessibility of the numerator events -- case series -- for the DSS case ascertainment scheme.

5.2 Accessibility of denominator events ("controls")

Lanctôt et al. found that 48% (14/29) of the drugs withdrawn were associated with other ADRs [9]. Spriet-Pourra & Auriche also found that there was not always a single reason for drug withdrawal; ADRs were associated with another safety reason, either ADR or experimental toxicity, in about one out of three cases, and multiple causes -- more than 2 ADRs -- were present in 12% of the cases [74].

A re-examination of Spriet-Pourra's & Auriche's data confirms that type B effects can indeed involve a single organ or be multisystemic. Although various type B events may share the same drug etiology, the magnitude of that sharing phenomenon seems to vary according to the type B effect category (Appendix 9.4). For example, 67% (4/6) of the dermatologic ADRs were associated with another type B event, as compared to 21% (3/14) of the hepatic ADRs. The data also indicate that, when a given drug use produces a type B toxicity, the toxicity appears to be limited to only one or a few organ systems.

That organ-specific toxicity may be related to the organ-specific metabolism of drugs coupled with the genetic polymorphism of the enzymes involved in the production and/or detoxification of the drugs' reactive metabolites [10(pp. 119 & 154)]. As a consequence, given an analytic focus on any specific type B event, it should be feasible to select, among the other type B events targeted by the DSS, those whose occurrence is judged to be independent of the drug use under study.

If a given hospital captures all of the set of targeted events, by their severe nature, these various AEs would tend to be similar as to the relevant factors that bear on their ultimate appearance in the hospital registry, meaning a shared catchment population. Valid sampling of the secondary source base can thus be achieved by selecting appropriate cases of an extraneous type B event from the same hospital registry, with admissible cases restricted to the local residents.

In other words, the accessibility of the denominator events is here again provided by the medical nature of the type B events themselves, the documentation of which provides for both the numerator and denominator series for etiologic research.

5.3 Accessibility of drug use histories

While medical practitioners are not usually interested in documenting the etiologic history, type B events on the contrary represent an unusual case as for the accessibility of drug use histories from the tertiary-care specialists. Indeed, from the medical practitioner standpoint, three particular medical aspects of the type B events call for a keen etiognostic interest and an urgent concern to ascertain the etiology of the AE: 1) Type B events are commonly drug-induced; 2) they tend to be acute, with the etiologic drug likely to be still in use at the time of the AE, thus, an urgent concern to remove it; 3) they tend to recur upon rechallenge, hence, a keen interest for etiognosis in order to properly advise the patient on avoidance of future drug use. Given that pragmatic motivation to go after the etiognosis and since the drug use issue is so important, the tertiary-care specialists should be concerned to document carefully not only the case per se but also the drug use

histories, leading to practice data of good research quality. In addition, since type B events tend to be acute with the etiologic drug use likely to be recent, details of "recent" drug use histories inclusive of non-prescription drugs would tend to be fully and reliably obtainable from the patient's recall, notably duration of use of all drugs since their initiation of use and duration since discontinuation.

Besides feasibility, the medical nature of the type B events also helps to assure the validity of the documentation of drug use histories. Since type B events tend to have a sudden/rapid onset, rather than insidious/gradual, potential changes in relevant exposure due to precursor or early stages of the AE would tend to be absent, that is, absence of a "protopathic bias" and presence of a valid setting for nonexperimental research on ADRs. The patients involved in each category of type B event are also likely to be equally concerned for their histories of drug use. With a data analysis stratified by hospital and admissible cases restricted to the local residents, the settings of interview would also be similar as to the milieu, the type of interviewer who is here the tertiary-care specialist, the mental condition and the socio-cultural characteristics of the subjects, meaning equi-accuracy of drug use histories across the different categories of type B event. Given that the targeted type B events can serve both as numerator and denominator series, assurance of equi-accuracy of drug use histories is also enhanced by the fact that the interviewer is inherently blinded as to the "outcome status" of case/noncase of the various type B events; additionally, both interviewers and patients are blinded as to the nature of the research hypothesis since all drug uses are recorded systematically in the context of routine clinical practice with no advance research hypothesis being formulated a priori.

6. SURVEILLANCE SYSTEM FOR TYPE B EFFECTS: A VISION

6.1 Overview of the system

Understanding of the considerations presented in chapters 3 to 5 leads, as an immediate corollary, to a vision in broadest outline of a DSS for the epidemiologic study of type B adverse effects.

For the DSS to provide for a rapid quantification of the adverse effect when a particular suspicion arises, the system must have pre-existing, research-quality data on that particular relation, data that cover the occurrence of that outcome event in relation to that drug use. In other words, the DSS must have already documented a large experience of type B AE occurrence, with the data ideally covering all drugs and all AEs in the population covered. Practically, for such a multipurpose coverage, the database would cover all drugs and a defined set of AEs that represents a high percentage of the type B events of concern, thus maximizing the probability of having the relevant data already available for immediate analysis. To that end, the system must secure a continual accrual of data on the occurrence of a defined set of AEs in relation to all drug uses in the population covered. This means the building up of a comprehensive, two-dimensional matrix of data, with the database established from the follow-up of a large catchment/candidate population for the defined set of type B events.

For the system to provide for an early signal of previously unsuspected effects as well as a sufficiently precise risk estimate with respect to newly marketed drugs, a good proportion of the early post-marketing experience with the new drugs has to be captured by the DSS. To this end, an even larger population coverage is needed such that the catchment population of the system's case ascertainment scheme covers a large proportion of the population to which the new drug is available. So for example, if only 10% of the population experience with a new drug is embedded within the DSS catchment population, large damage would be done with many unnecessary tragedies from the new drug before the DSS captures the ADR signal.

Fortunately, the limited number of type B events -- and their related specialties -- of concern, a dozen or so, together with the small number of presumably highly motivated tertiary-care specialists who are involved with their routine medical management, allow outstandingly for the operational capture of such a desired experience of type B AE occurrence, with respect to a very large catchment population for a quite comprehensive set of type B events.

To that operational end, after defining the set of AEs of principal concern, one needs to enroll a large network of suitable participating tertiary-care hospitals. The participating hospitals need to have all -- or most -- of the relevant subspecialties that relate to the targeted set of AEs. Additionally, all -- or most -- of the tertiary-care specialists working in these relevant specialties at the participating hospitals need to be also willing to participate. Then, for each and all of the accruing cases of the targeted AEs, the participating specialists will record data on the outcome event and the drug use histories, in the context of their routine medical care. These data records, likely to be of good research quality, will then be submitted to a central facility for data processing. Given the medical particulars of the type B AEs, continual and systematic accumulation of these data records at the central facility -- using the same logistic and organizational framework for each of the different type B events -- provides for both the numerator and denominator series for etiologic research.

Regular screening of this large quantity of data would provide the DSS with the capability of generating early signals of type B ADRs. Additionally, there is also a good chance for the multipurpose research system to have the relevant data available for a timely and scientific quantification of any alleged type B effect, whenever a suspicion arises from within or outside of the system. Such a quantification of suspected adverse effects would be not only rapid but also valid and precise.

6.2 Particulars

6.2.1 Access to numerator and denominator series

Given that overall vision, the need remains to identify the means of getting the collaboration of the tertiary-care hospitals and the tertiary-care specialists, and to define tentatively a set of type B events to be targeted by the DSS.

The issue of confidentiality may be raised by some regulators/administrators as for the sharing of the data records with the DSS, and/or the access of the DSS research personnel to the rosters of patients with these type B AEs for auditing purposes. In Europe, a directive from the European Communities Council regarding the confidentiality of databases has been recently proposed with an aim for a better protection of the individuals' personal data. Concern has been raised, however, by many research organizations regarding the negative impact of that directive on drug safety assessment, and regarding the questionable ethics of not using information already collected to improve drug safety in the community [85]. Ethically speaking, from the patient point of view, it would be fair to think, indeed, that patients would not object to the fact that their iatrogenic illnesses be reported, and that the likely objectors, if any, would rather be the medical practitioners themselves for fear of potential legal implications. As a proposition, since risk of type B ADRs is a serious public-health concern, regulators/administrators, as well as practitioners and patients, should consider that problem of confidentiality as an exceptional nonissue.

Since mandatory reporting of ADRs is already required in some countries, like France, and since type B ADRs represent such a serious aspect of drug-induced illnesses, regulators should also require a mandatory reporting of a selected set of type B events by all tertiary-care specialists, with no causal attribution to entertain in the reporting. That setting of a mandatory reporting, as with unexpected hospital deaths that need to be reviewed per regulatory requirement, would serve the public-health safety surveillance concern regarding these serious AEs. By the same token, the setting of a mandatory

reporting would increase dramatically the feasibility of recruiting participating centers to the DSS; it would also help to assure the completeness of the AE reporting by the tertiary-care specialists to the DSS registry, as compared to the DSS just counting on the good will of the participating medical practitioners. Data from these regulatory reports will also provide a valuable cross-check on the DSS registry data.

Whether required by regulators or not, given their pragmatic motivation for etiognosis, the tertiary-care specialists should be concerned to submit the patient record to a central facility that would supply the probabilities, evidence-based, that a recent drug use caused the patient's AE. Such a possibility for the clinical specialist to consult with an "expert" surveillance system should be inherently welcomed on the basis that he/she has an ethical and a professional responsibility to tell the patient about the probabilities of such causation. To that end, however, the clinical practitioner commonly lacks conceptual and factual knowledge for setting up an etiognostic probability for the case at hand, with consequently for him/her a great sense of helplessness and for the patient an unresolved threat.

Additionally, per their academic training, these specialists' scientific orientation should constitute another reason for their willingness to share their practice records with a research system that is devoted to the advancement of scientific knowledge about type B risk assessment. A monetary reward, payable to the participating institution and/or the tertiary-care specialists themselves, may also be considered.

Although it would be more efficient to enroll tertiary-care hospitals that have all of the relevant specialties related to the targeted set of AEs, it is not an absolute requirement. Indeed, given a particular hypothesis, valid analysis -- stratified by hospital -- can still be carried out using only data from those hospitals that happen to have the relevant numerator series coupled with an appropriate denominator series for that particular "AE-drug use" relation. Similarly, it is not absolutely necessary to obtain the participation of all the tertiary-care specialists working in a given specialty at a participating hospital. Indeed, the specialist who participates will still provide a fair/determinant-representative

sample/subset of all cases of type B events that relate to his/her subspecialty, since it is very unlikely to think of a situation in which drug users (index cases) would be mainly treated by one specialist and non-users (reference cases) mainly treated by another specialist.

As for the set of type B events of concern, Lawson, in 1990, has suggested an instructive list of 15 rare conditions, commonly iatrogenic, affecting eight organ systems and considered suitable for enrolling in "case-registry studies" for possible drug etiologies [17]: 1) Haematologic: acute haemolytic anemia, agranulocytosis, aplastic anemia; 2) Hepatic: acute hepatic necrosis, toxic hepatitis; 3) Neurologic: Guillain-Barré syndrome; 4) Renal: acute renal failure, acute interstitial nephritis; 5) Dermatologic: Stevens-Johnson syndrome, toxic epidermal necrolysis, dermatomyositis; 6) Ophthalmologic: acute glaucoma, retinal degeneration; 7) Cardiovascular: primary pulmonary hypertension; and, 8) Gastro-intestinal: retroperitoneal fibrosis. Anaphylactoid events and thrombocytopenic purpura have also been suggested for etiologic study [44]. Since all of these 10 categories of type B effects and most of these 17 illnesses have been associated with drug withdrawals (Appendix 9.4), this list represents a good point of departure for the delineation of a more limited set of type B events to be targeted by the DSS. That limited set would likely include agranulocytosis and aplastic anemia [14], toxic epidermal necrolysis and Stevens-Johnson syndrome [15], primary pulmonary hypertension [82], thrombocytopenic purpura and anaphylactoid reactions [44], as well as Guillain-Barré syndrome [75], since all of these eight AEs have already been the object of large scale ad hoc case-control studies.

6.2.2 Access to drug use histories and other data

Given their pragmatic -- etiognosis-driven -- motivation and their scientific interest, the tertiary-care specialists represent an outstanding source of international cooperation for a continual accrual of type B-related data records with high quality information. Besides the patient characteristics routinely recorded on admission such as patient demographics and medical history, these super-specialists would likely supply practice-based information that

is relevant for the researcher, including careful documentation of the outcome-event diagnosis, the drug use histories, modifiers that relate to sub-domain issues, and potential confounders. Notable among the modifiers is the duration of previous drug use, and among the potential confounders are the other drug uses etiologic for the AE at issue.

A possible limitation to the quality of the DSS data records relates to the fact that indication of the various drug uses may not be an inherent concern for documentation from the medical practitioner standpoint. That issue would not be so important, however, because confounding by indication tends to be rare in the study of adverse effects, given their unlikely association with the indication. The subject's degree of "medicalization" would be rather difficult to document, but the issue of confounding by medicalization would be dealt with directly by an accurate documentation of all recent drug uses with a view to a thorough control in the analysis. Confounding by contra-indications is commonly a nonissue in type B drug risk assessment, since contra-indications are uncommon in themselves and rarely bear on the risk of the type B events.

To increase furthermore the research quality of the data records, steps would also be taken to ensure that all data are uniformly recorded by the participating tertiary-care specialists, according to a common protocol. Drug use histories, including duration of recent use and previous use of both prescription and nonprescription drugs, would be obtained from the patient's systematic interview by the tertiary-care specialist, using pre-designed, standardized data collection forms.

Information from the data collection forms would be corroborated by data abstracted from the patient medical records and the pharmacy prescription records such as the pharmacy drug dispensation/reimbursement files. Such record abstraction would be carried out per standardized abstraction protocol. Settings with computerized medical and pharmacy records would be given priority in the deployment of the surveillance system.

6.3 General features of the system

6.3.1 Structure

Since each of the participating centers/institutions needs to capture the whole set of type B AEs targeted by the DSS, or most of it, they are likely to be university-affiliated tertiary-care institutions. Since the catchment population of the DSS for the targeted AEs needs to be large, 100 million persons or more, the participating hospitals are likely to be scattered across many countries. Such a large network would require a coordinating center/central facility, equipped with effective means of communication, such as a toll-free telephone number, computer conferencing, etc.

6.3.2 Functions

6.3.2.1 Participating centers

The participating centers will be responsible for keeping up to date rosters of all patients with the targeted type B events. They would also perform data editing to ensure completeness, consistency, and accuracy of the data records, before submitting these data records together with the corresponding medical and pharmacy records to the coordinating center for data processing.

In the context of their routine medical care of each and all of the targeted type B AEs, the tertiary-care specialists will be responsible for completing themselves the original data records, with diligent and proper implementation of the appropriate diagnostic and interview protocols and any additional means of validity assurance, in accord with the instructions from the coordinating center.

6.3.2.2 Central facility

The central scientific staff would be responsible for the research training of the participating tertiary-care specialists, the elaboration of standardized protocols and data collection forms, the supply of evidence-based etiognostic probabilities back to the specialists, the implementation of auditing procedures, and the whole process of data processing-analysis-reporting.

Data processing includes data cross-checking, coding and storage in a readily retrievable form. A built-in quality-control program, to continuously assure the maintenance of uniform standards of data collection, is absolutely essential; it will be supplemented with suitable routine computer checks of the data for completeness, plausibility, and internal consistency. Data analysis will be carried out regularly with a view to hypothesis generation, while hypothesis testing/effect quantification will be carried out on an as needed basis. Since a multitude of associations tends to appear with the regular screening of the data, clear guidelines on how to set priorities for detailed subsequent analyses have to be elaborated [42]. With respect to potential confounding, accent will be placed on its prevention rather than its control, notably by selecting an appropriate population and/or treatment contrast such that the potential confounders are equally associated with each category of the population/determinant contrast(s). Finally, regular technical and scientific publications that provide updates on the system's activities should be encouraged as a feedback to the participating centers as well as to the scientific community.

Means of validity assurance with respect to the outcome documentation need to be elaborated by the coordinating center in order to assure that the process that brings cases to the DSS central registry is independent of drug use history; that requirement is a requisite condition for the feasibility of valid sampling of the secondary source base. Such assurance is already achieved, for one, by the severe nature of the type B AEs themselves which provides for a complete case hospitalization. Assurance is further enhanced by the following additional means: 1) elaboration and implementation of a mandatory, standardized diagnostic protocol for the set of targeted type B events with

respect to standardized AE definition, diagnostic criteria, and diagnostic procedures; 2) lobbying for the implementation of a mandatory reporting scheme for these AEs to regulatory agencies; and, 3) elaboration and implementation of auditing procedures. These various operational means will help to assure the completeness of case diagnosis in the hospital setting as well as subsequent "registration" at the DSS central facility, thus providing for an unbiased case ascertainment and also the setting of a "population-based" registry which would yield a more precise estimate of the incidence-density rates for the AEs at issue. Lastly, given a possibility of failure to achieve a 100% case diagnosis and reporting to the central registry, a swift analysis of the data already collected when the first suspicion arises and before awareness of the ADR hypothesis spreads will also enhance equi-accuracy of the case ascertainment process.

Auditing procedures need to be planned ahead in order to ensure the completeness and accuracy of the reports provided by the participating centers. Diagnostic auditing that targets all possible sources of potential cases, with observer blinding when feasible, will help to assure the completeness of case diagnosis, i.e., decrease the number of missed cases (false negatives); on the other hand, auditing the records of cases already diagnosed by routine health-care practice will increase the accuracy of case diagnosis, i.e., decrease the number of false cases (false positives). Although both the missed and the false cases would tend to occur in the reference category of the drug exposure, auditing priority should be given to reduce the former since the problem of missed cases would tend to be more prevalent and bias the result towards the presence of an adverse effect that may not actually exist, while the problem of false cases would tend to be less prevalent and only dilute an eventual adverse effect that truly exists. To that end, files of hospital discharges should be checked for example by the DSS research personnel. Auditing the log of all possible sources of records of diagnosed cases will assure the completeness of case reporting to the central registry. In that respect, the DSS research personnel should be keen to check regularly the hospital and regulatory rosters of patients with the type B events to ensure that all cases have been actually reported to the DSS. Finally, the documented drug use histories and other clinical data should be cross-checked with the patient medical records and pharmacy prescription records.

6.4 Responsiveness of the system

The envisioned DSS would be very much responsive to the current problem of noninformed banning/withdrawal of drugs when regulatory crises arise from suspicions of previously unsuspected type B ADRs. Indeed, at any time, were a particular hypothesis to occur, there should be a good chance of having, within the DSS database, pre-existing, research-quality data on the occurrence of the AE at issue, on the drug use of concern -- even for a newly marketed drug, on a valid denominator series, coupled with appropriate information on covariates and a quantity of data large enough for suitable precision in the immediate quantification of the adverse effect. In the nonemergency situation, the continuously accumulated data would be regularly screened for hypothesis generation, with swift effect quantification whenever a suspicion arises.

7. DISCUSSION

7.1 Some prevailing concerns

There are some prevailing concerns that pertain to the "case surveillance" approach and the use of case-registry data in drug risk assessment, a topic that may be considered as closely related to the DSS design. These concerns commonly held about case registries may be summarized as follows: 1) possibility of biased and/or inaccurate case ascertainment [15,19]; 2) absence of a control group for a valid quantification of risks [15,19,44,76] and feasibility problems in the recruitment of appropriate controls [76,77]; 3) feasibility problems in routine collection of reliable and full drug histories from patients [19,44]; 4) feasibility problems in adequate control of confounding without direct access to patients and without detailed information obtained by interviews [15,44]; 5) problems in the selection of illnesses for additional registries [18,19]; 6) feasibility problems in data pooling across international registries [19]; 7) inappropriateness of the use of same data for both hypothesis generation and hypothesis testing, with the former performed by regular case-control screening, with the involved analysis adjusted for multiple comparisons and sequential testing [22]; and 8) need for cost-benefit analysis

of maintaining disease databases, with adequate controls, for rapid risk assessment [77].

Many of these expressed concerns, however, would not apply inherently to the envisioned DSS, which differs from and should not be viewed as the network/series of separate case-registries that has been advocated with the case surveillance approach. These concerns are reviewed in brief below, in the lights of what has been presented in chapters 4, 5 and 6.

Possibility of a "biased"/inaccurate case ascertainment. That issue has to do with the validity requirement of completeness of outcome documentation, or at least its equi-accuracy -- equal degree of freedom from error -- between the contrasted categories of the determinant; that is, a passive case accrual or an active case ascertainment process independent of the history of drug use. The related principles of validity assurance are presented in section 4.4.2.1. That requirement is a requisite condition for the feasibility of valid sampling of the secondary source base (section 4.3). Means of validity assurance that need to be elaborated by the coordinating center, in order to assure that the process that brings cases to the DSS central registry is independent of drug use history, are presented in section 6.3.2.2.

Absence of "control groups" and choice of appropriate "controls". This concern is a nonissue here, since the DSS is targeting simultaneously a set of type B events, with the corresponding data records submitted by tertiary-care specialists affiliated with a network of participating tertiary-care hospitals. Continual accumulation of the data records at the central facility -- using the same logistic and organizational framework for each of the different type B events -- provides for the denominator series as well as the numerator series. The issue of appropriate "controls" has to do with the validity requirement of representative sampling of the source base for the first-stage denominator series -- representative as for the distribution of the drug use history, either within the source base at large or within each of the confounder/modifier strata accounted for in the analysis. The related principles of validity assurance are presented in section 4.4.2.2. Discussion on the accessibility of denominator events ("controls") and the DSS access to the

denominator series is presented in sections 5.2 and 6.2.1.

Problems in routine collection of reliable and full drug use histories. That comment does not seem to appreciate the medical particulars of the type B AEs that are treated by highly motivated tertiary-care specialists. Moreover, the comment would not apply to the context of a DSS that would supply etiognostic probabilities upon reception of the data records. Finally, that comment addresses the validity requirement of completeness of documentation of drug use history, or at least its equi-accuracy between the numerator and denominator series; that is, drug use record abstraction, interview process, and patient recall independent of the outcome status (case, noncase). The related principles of validity assurance are presented in section 4.4.2.3. Discussion on the accessibility of drug use histories and the DSS access to the drug use histories is presented in sections 5.3 and 6.2.2.

Although it could be argued that it may be too optimistic to think that the busy tertiary-care specialists would be willing to document drug use histories whenever AEs under surveillance occur in their practices, it just seems to me that such a professional attitude could be easily promoted and advocated, or even regulatory requested via mandatory reporting, given that these commonly drug-induced AEs are not so many and occur not so frequently, and that each patient experiencing these serious events should deserve the best possible care from each medical practitioner.

Another related argument would be that some tertiary-care specialists may be loath to implicate their colleagues by reporting drug use prescribed by those colleagues. If it is the first time that a patient experiences the type B event, these colleagues who have prescribed the various drug regimens to the patient cannot be held responsible since the patient's contraindications to the etiologic drug use were not knowable in the first place. Moreover, it is in that type of situation that the tertiary-care specialists should feel compelled to take detailed drug use histories for a subsequent consultation with the DSS central facility which would supply the drug etiognostic probabilities, thus helping their

colleagues to avoid future prescription of the culprit drug or helping the patient to avoid future use of the etiologic nonprescription drug.

Problem of control of confounding without detailed information from patient interview. This comment applies only to data obtained from automated databases. The context here is the very opposite, the specialists facing and interviewing their patients with a keen concern about etiognosis. The principles of validity assurance regarding potential confounding, that is, absence or control of differences between the index and reference subpopulations in terms of extraneous determinants of the AE risk, notably with respect to contraindications and exposures to other etiologic drugs, are presented in section 4.4.2.4. The issue of the DSS access to data on potential confounders is presented in section 6.2.2.

Selection of Illnesses to be registered. A list of 17 illnesses, most of which having been associated with drug withdrawals, is presented in section 6.2.1, and represents a good point of departure for the delineation of a more limited set of type B events to be targeted by the DSS.

Problems in data pooling across international registries. That comment seems to refer to the problem of harmonization of the data content of and the computer format/medium for the electronic data records that are developed independently in different countries. This topic is currently addressed by committees on international data standards for hospital-based drug surveillance in the context of automated patient care data [78]. It would not apply, however, in the context of the DSS where tertiary-care specialists interview and submit their data records to the DSS central facility according to a common protocol.

Data analysis from the "frequentist" outlook. With respect to data analysis, Bayesian inference outlooks are the ones that I would strongly recommend to the developers of the DSS for adoption in their presentation of the evidence pertaining to estimates of drug risks. Indeed, many frequentist notions about inference, including the notion of

inappropriateness of the use of same data for both hypothesis generation and hypothesis testing, are misguided. Thus, from the Bayesian vantage [16 (p. 116),64]: 1) testing "data-suggested" hypotheses with the very same data is entirely valid, meaning, there is no need for new data for proper (actual) testing; 2) testing multiple, uncorrelated hypotheses within a single study is totally appropriate, meaning, there is no need for the P-values to be "corrected" when more than one hypothesis are tested; and 3) sequential testing of the same hypothesis, ignoring the number of tests, is also appropriate, again meaning, there is no need for P-values to be "corrected" for repeated testings of a hypothesis in the course of continuous data accrual. These considerations are quite important for the process of regular data analysis which is performed within the DSS for hypothesis generation, with immediate hypothesis testing/effect quantification as needed.

Additionally, in drug risk assessment, the essence of epidemiologic inference is to update, in the light of the empirical data, the prior view about possible values of the theoretical quantity IDD (incidence density difference), and to derive an updated posterior view, with no conclusion of "acceptance" or "rejection" to be declared. The prior view, based on subjective insights from basic sciences or from previous drug experience -- formal or informal, provides for a distribution of prior probabilities P_i' for a range of possible values IDD_i including the null value. The likelihood function, as implied by the chi-square function, gives the likelihood (L_i) of the datum idd* as a function of the hypothesized values IDD_i , and provides for the derivation of the cumulative distribution of posterior probabilities P_i'' for the hypothesized range of values IDD_i , per Bayes' theorem: $P_i'' = P_i'L_i / \Sigma_i P_i'L_i$. Under Bayesian analysis, both hypothesis testing and estimation are then read directly from the cumulative posterior probability distribution. For hypothesis testing, the posterior probability for a hypothesized range of IDD_i is the sum of the posterior probabilities P_i'' over that range. The point estimate is the median of the cumulative posterior probability distribution. For $(1-\alpha)$ probability interval estimation, the lower and upper bounds correspond to the cumulative posterior probability values of $\alpha/2$ and $1-(\alpha/2)$ respectively.

Cost-benefit of "disease databases" for rapid risk assessment. Given the status quo of type B drug risk assessment (section 1.5) with respect to a rapid response upon a signal generation, there is currently no alternative to the proposed vision. The ultimate "test" for cost-benefit analysis of the DSS would be to determine whether industry would be willing to invest in the implementation of the vision. Industry and governmental funding for the deployment of the proposed DSS are very much called for on the grounds that government and industry are the two key players who have to take important decisions about drug banning/withdrawal or relabelling. While government interest in drug risk assessment derives from its responsibility for societal risk management, a pharmaceutical manufacturer's involvement in the deployment of the DSS has inherently major positive implications [18,79]. Such a data system can obviate inclusion of pseudo-adverse effects in package inserts, help in litigation, obviate drug withdrawal/banning. In short, it can provide an opportunity to protect and expand the use of the manufacturer's products. It is important to note that drug withdrawals for reasons related to safety have increased from a rate of 2.2 products per year prior to 1983 to 8.6 products per year thereafter, with no apparent increase in the number of new product launches [74]. Lastly, it would seem fair to say that the system should be far less expensive than setting up separate international ad hoc "case-control" studies with different "controls" selected for each type B event studied, as is currently being done.

Besides the provision for the epidemiologic study of type B effects, the DSS will also provide a precious setting for the study of the clinical, therapeutic, pathologic, and genetic aspects of the type B AEs, with an ultimate benefit to both public health and patient care.

7.2 Future work

While I have set forth the general vision of a DSS for type B effects and some of the particulars and general features of the system, many important topics remain to be addressed. They include, among others: the identification of the final set of type B AEs to be targeted by the system together with an international harmonization of the AE definition, diagnostic criteria, and diagnostic procedures; the design of appropriate data

collection forms together with a standardized interview protocol; and the design of a standardized protocol for abstraction of data from the patient medical records and the pharmacy prescription records. For example, the diagnosis of toxic epidermal necrolysis, a rare but severe, acute cutaneous reaction and commonly drug-induced, has presented some difficulties in terms of its boundary with Stevens-Johnson syndrome [80], in the context of an ongoing international "case-control" study of these two entities [15]. With respect to the design of data collection forms for routine monitoring of the type B events, considerations should be given to the relevance of the information item to be collected as well as the "cost" and accuracy with which it can be obtained [42].

Issues like how the DSS would contribute to clinical etiognosis, scientific publication and public policy, or what are the key aspects of the system's personnel, logistics, finance and organization, also represent important considerations to be addressed. In addressing these issues, discussion and collaboration with the many existing international foundations and organizations also concerned with drug risk/safety should be encouraged. These organizations include, among others, the International Medical Benefit/Risk Foundation [81], the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring [77], and the Council for International Organizations of Medical Sciences (CIOMS) [13].

8. CONCLUSION

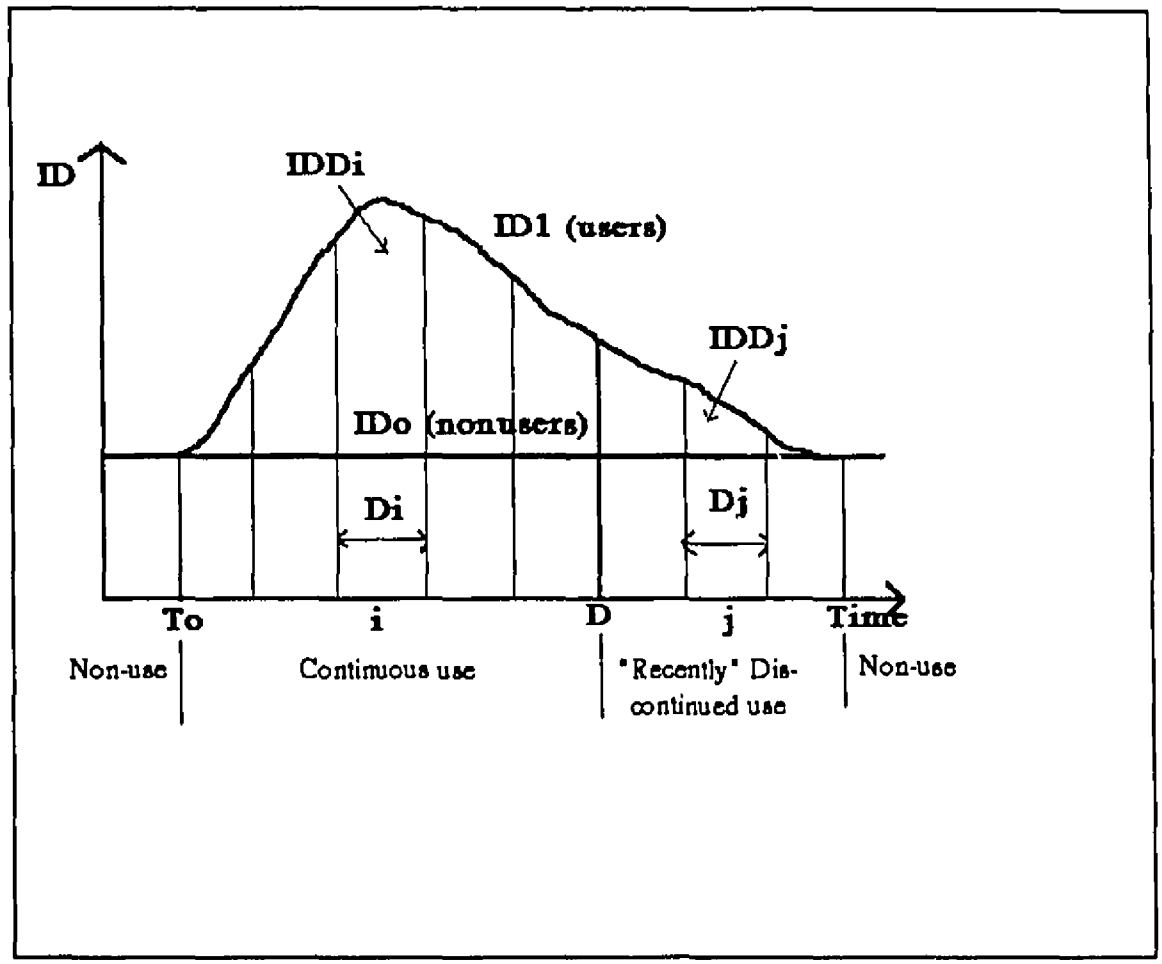
Risk assessment with respect to type B adverse effects of drugs is still wanting, as there remains a dramatic lack of pre-existing systems of data available for immediate analysis at the time that the suspicion arises, with unwarranted bannings or withdrawals of drugs the consequence of this. Without any sound information base, investments of hundreds of millions of dollars per drug are thus sacrificed, and effective and also possibly safe drugs are withdrawn or banned almost overnight. On the other hand, many other adverse effects of public health importance may still go unrecognized or are discovered only with much delay. To answer the challenge, I have proposed a solution which consists of a drug surveillance system, international in scope, targeting simultaneously a set of type B events commonly related to regulatory decisions about drug withdrawals. The system involves ongoing, systematic recording of outcome events and drug uses, with the data records submitted to a central facility by tertiary-care specialists affiliated with a network of participating tertiary-care hospitals. Upon reception of these data records, the central facility would supply the probabilities, evidence-based, that a recent drug use caused the patient's adverse event. Continual accumulation of these data records at the central facility -- using the same logistic and organizational framework for each of the different type B events -- provides for both the numerator and denominator series for etiologic research. The envisioned system should deserve close attention from those forward-thinking decision makers concerned to have provision for early signals of previously unsuspected type B adverse reactions, as well as quantification of suspected effects that is not only rapid but also valid and precise. The proposed program of data collection, processing and analysis should provide for rapid resolution of crises arising from novel suspicions of type B effects, even with respect to newly marketed drugs.

9. APPENDICES

9.1 Assessment of Type B Excess Risks (adapted from references 61,62)

(in terms of incidence density differences (IDDs) specific to subintervals of the total risk period, subsequent to the initiation of the drug use, conditionally on confounders and modifiers).

For the contemplated duration of use D, drug risk -- the total ADR risk (R_D), is approximately the sum of the risk differences over the intervals during and after the contemplated use of the drug: $R_D \approx \Sigma_i (ID_{1i} - ID_{0i})D_i + \Sigma_j (ID_{1j} - ID_{0j})D_j$



ID_1 : (index) incidence density of the type B event among the "recent" users (first use)

ID_0 : (reference) incidence density of the type B event among the nonusers (presumed constant during the short period of follow-up)

D_i : i^{th} time interval during the period D of continuous use

D_j : j^{th} time interval during the period of "recently" discontinued use (after period D)

T_0 : zero time defining the drug intervention -- scientific, cohort -- time scale

9.2 Meta-experiment: Overall incidence density difference idd*

(adapted from reference 64)

Confounder stratum j	Subcategories of "recent exposure"		
	INDEX	REFERENCE	OTHER
Numerator events (cases) c"j	c1j	c0j	c'j
Denominator events ("controls") d"j	d1j	d0j	d'j
Total number of events t"j	t1j	t0j	t'j
Source population-time D"j	D1j	D0j	D'j
Actual incidence density rates idj	id1j=c1j/D1j	id0j=c0j/D0j	
Quasi-incidence density rates id'j	id'1j=c1j/d1j	id'0j=c0j/d0j	

c"j : total number of cases in the first stage numerator series, in the jth stratum = c1j+c0j+c'j

d"j : total number of probes into the source population-time, in the jth stratum = d1j+d0j+d'j

D"j : source population-time of follow-up (source base), in the jth stratum = D1j+D0j+D'j

R"j : source population incidence density (ID) rate (theoretical) , in the jth stratum = c"j / D"j

Given stochastic proportionality of the denominator probing (source-base sampling):

d1j/D1j = d0j/D0j = d"j/D"j ; therefore,

Index incidence density in stratum j : id1j = (c1j/ d1j) (d"j/D"j) = id'1j (d"j/D"j)

Reference incid.density in stratum j : id0j = (c0j/d0j) (d"j/D"j) = id'0j (d"j/D"j)

Thus, equality of incid.density ratio (idrj), quasi-incid.density ratio (qidrj), and "odds ratio" (orj)

idrj = id1j/id0j = id'1j/id'0j = qidrj = (c1j/d1j) / (c0j/d0j) = c1jd0j/c0jd1j = orj

Incidence density difference in stratum j (iddj) versus quasi-incid.density difference (qiddj)

iddj= qiddj (d"j/D"j)= (c1j/d1j - c0j/d0j) (d"j/D"j)= (c1jd0j - c0jd1j) (d"j/D"j) / (d1jd0j)

Overall incidence density difference across the confounder strata j (idd*)

Using the following weights (Wj) for idd*: Wj =1 / (tj-1) (d"j/D"j) R"j (with tj=t1j+t0j)

idd*= SUM j [(c1jd0j -c0jd1j) / (tj-1)R"j] / SUM j [d1jd0j / (tj-1) (d"j/D"j) R"j]

9.3 Type B risk assessment: size of source population (adapted from reference 62)

In the assessment of excess risk in terms of incidence density difference (IDD), the empirical index rate (id_1) is critical because the index population-time (D_1) is small compared to the reference population-time (D_0), due to rare exposure of the catchment population to the drug at issue (index exposure). Since the cases of type B event are rare and the positive history is also rare, a major determinant of the precision of the index rate is the (Poisson) expected number of "recently" exposed cases (E_{c1}); that is the expected number of cases in the index population-time (not the denominator). E_{c1} alone determines the coefficient of variation (CV) of the estimate of average risk of use (risk over average risk period) -- in terms of average incidence-density (ID_1):

E_{c1}	CV_{id1}
10	32%
50	14%
250	6%

$CV_{id1} = SD_{id1} / ID_1 = (E_{c1}/D_1^2)^{1/2} / (E_{c1}/D_1) = (E_{c1})^{-1/2}$

SD_{id1} : standard deviation of the empirical index incidence density id_1

ID_1 : theoretical index incidence density ($ID_1 = E_{c1}/D_1$)

D_1 : (index) population-time of follow-up for the exposed catchment-population

For the parameter of ultimate concern IDD, an added determinant of precision is the rate ratio (incidence-density ratio, $IDR = ID_1/ID_0$) :

E_{c1}	IDR	CV_{idd}
50	∞	14%
	10	16%
	2	28%
250	∞	6%
	10	7%
	2	13%

$CV_{idd} = SD_{idd} / IDD = [(E_{c1}/D_1^2) + (E_{c0}/D_0^2)]^{1/2} / [(E_{c1}/D_1) - (E_{c0}/D_0)]$

$CV_{idd} = [(ID_0(IDR)/D_1) + (ID_0/D_0)]^{1/2} / [ID_0(IDR) - ID_0]$

$= [(IDR/D_1) + (1/D_0)]^{1/2} / (IDR-1)(ID_0)^{1/2}$

$\simeq [IDR/D_1]^{1/2} / (IDR-1)(ID_0)^{1/2} = [IDR^{1/2}/(IDR-1)] / D_1^{1/2} (ID_0)^{1/2}$

$= [IDR^{1/2}/(IDR-1)] / D_1^{1/2} (ID_1/IDR)^{1/2} = [IDR^{1/2}/(IDR-1)] / [(E_{t1})^{1/2} / IDR^{1/2}]$

$CV_{idd} = [IDR/(IDR-1)] / (E_{t1})^{1/2}$

SD_{idd} : standard deviation of the empirical incidence density difference idd

IDD : theoretical incidence density difference ($IDD = ID_1 - ID_0$)

ID_0 : theoretical reference incidence density ($ID_0 = E_{t0}/D_0$)

E_{t0} : expected number of "recently" unexposed (reference) cases

D_0 : (reference) population-time of follow-up for the unexposed catchment-population

The expected number of "recently" exposed cases (E_{t1}) may be derived from the prevalence ($P = D_1 / D'$) of "recent" use in the catchment population, together with the catchment population-time of follow-up (D') :

$$E_{t1} = PD' (ID_0) (IDR)$$

Bellwether example : $ID_0 = 10/10^6$y (cf. agranulocytosis), IDR = 5. To obtain $E_{t1} = 250$ requires, for various values of P :

P	D'
0.1%	5000 (10^6y)
1%	500 (10^6y)
10%	50 (10^6y)
(cohort of users) 100%	5 (10^6y)

Thus, to obtain $E_{t1} = 250$ in the context of $ID_0 = 10/10^6$y, IDR = 5, and P = 1% prevalence of "recent" use, one would be required to follow-up over 5 years a source population of size 100 million persons, i.e., one would need to have a source base $D' = 500$ (10^6y).

9.4 Categories of type B effects associated with drug withdrawals

Note: Figures are recalculated from reference 74 and differ slightly from those listed in the original reference, since in my computation of type B-related drug withdrawals, I have left out the authors' original categories of gastro-intestinal effects from NSAIDs, endocrinological effects from steroids, metabolic effects from antidiabetics, and the categories of poisoning and abuse from drug misuse, that is, the type A adverse effects.

Of a total of 80 safety-related drug withdrawals (DWs) between 1961 and 1987 (FRG, France, UK, USA), 65 (81%) are concerned with clinical ADRs, 10 (13%) with experimental toxicity, and 5 (16%) with manufacturing problems.

90% (57/65) of the ADR-related DWs concerned type B effects which can involve a single organ or be multisystemic. Of the 57 cases of type B DW, another type B event was implicated in 12% (7/57) of the cases (double-ADR/DADR), while more than 2 type B events were present in 11% (6/57) of the cases of drug withdrawal (multiple-ADR/ MADR).

10 "organ-specific" categories of type B effects were associated with DWs:

1- hepatic: 14 DWs [2 DADR (1haemat., 1neurol.) +1 MADR; i.e. **21%** (3/14) >1 ADR]
2- haematologic: 12 DWs [2 DADR (1hepat., 1dermat.) +2 MADR; i.e. **33%** (4/12) >1 ADR]
3- neurologic: 11 DWs [3 DADR (1hepat., 1dermat., 1coagul.); i.e. **27%** (3/11) >1 ADR]
4- dermatologic: 6 DWs [4 DADR (1haemat., 1neurol., 1opht., 1renal); i.e. **67%** (4/6) >1 ADR]
5- ophthalmologic: 4 DWs [1 DADR (dermat.) +1 MADR; i.e. **50%** (2/4) >1 ADR]
6- allergic: 4 DWs
7- cardiovascular: 4 DWs
8- nephrologic: 3 DWs [1 DADR (dermat.); i.e. **33%** (1/3) >1 ADR]
9- teratogenic: 2 DWs
10- coagulation disorders: 1 DW [1 DADR (neurol.); i.e. **100%** (1/1) >1 ADR]
(11- multiple ADRs: 6 DWs)

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