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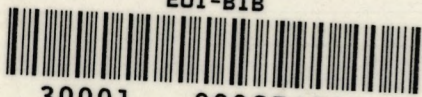
**The Regulation of Drug Development:
In Search of a Common European Approach**

ERICH KAUFER

European University Institute, Florence

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BADIA FIESOLANA, SAN DOMENICO (FI)

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Printed in Italy in October 1989
European University Institute
Badia Fiesolana
– 50016 San Domenico (FI) –
Italy

The Regulation of Drug Development: In Search of a Common European Approach

by

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Second Draft: October 1989

The European Policy Unit

The European Policy Unit at the European University Institute was created to further three main goals. First, to continue the development of the European University Institute as a forum for critical discussion of key items on the Community agenda. Second, to enhance the documentation available to scholars of European affairs. Third, to sponsor individual research projects on topics of current interest to the European Communities. Both as in-depth background studies and as policy analyses in their own right, these projects should prove valuable to Community policy-making.

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A. The Regulation of Drug Development in Europe:

A Statement of the Problem

The regulation of drug development in the European Community is at a crossroad. The White Paper on the Completion of the Internal Market states:

"The internal market shall comprise an area without internal frontiers in which the free movement of goods, persons and capital is ensured in accordance with the provisions of the Treaty". <5>

This goal should be achieved by 1993. However, formidable barriers exist for the achievement of this goal in the case of medicinal products. These barriers have deep historical roots, and because the roots are historical, they are specific to the traditions of each individual member state. <9;15;25;42;54>

The regulation of the supply of drugs is a multi-layered process, because it is an exceptional blend of actual or suspected sources of market failure. Firstly, drugs are products characterized by credence qualities <25;35;36>. It is suspected that bad qualities drive good qualities from the market. Secondly, the supply of drugs is thought to be subjected to propensities to monopolize due to the price inelasticity of demand. Thirdly, the demand for drugs is plagued by principal-agent problems. <6;25;26>

(1) Medical theories have changed over the centuries. But for millennia a secular constant has been the concern over the purity of the ingredients of the medicinal preparations. Galen, the physician of the Emperor Marcus Aurelius Antoninus was so obsessed by the fear of adulterated bulk material that he hired an adulteror of drugs in order to learn how to protect himself against adulteration. And in the 20s of our century, when the drug companies were still mostly producers of herbal bulkware, *branded* herbal bulkware carried prices up to four times higher than the *generic* one. The argument then has been: superior and assured quality. The counter-argument has been: the formulations of the *Pharmacopeia* set controllable standards, so that the price differentials are unjustified. The situation today is quite similar. There is as great a concern about "adulterated" drugs as during Galen's or our grandfathers' time. Branded products are much more expensive than generic ones. But has not drug regulation been brought in, in order to set controllable standards? <47;48>

(2) Up to the 1920's, even the 1930's, the main source of monopoly power of the drug supplier may be called quality ignorance of the patient. At that time most drugs, except narcotic and highly toxic ones, could be

bought without a prescription by the physician. Drug companies, therefore, directed their advertisements directly to the patients or to the pharmacists. This changed with the advent of the wonder-drugs. Firstly, they were highly potent and, therefore, in Paracelsus' words highly *useful poisons*. To protect the patient against poisoning himself he had to be restricted by the physician's prescription. Secondly, the new drugs were curative and life-saving. For that reason the price elasticity of demand declined sharply. In response, a marked tendency to monopolize is predicted by economic theory. Is the prediction supported by changes in market structure?

Prior to the advent of the antibiotics most drug manufacturers were mere suppliers of bulkware. The first antibiotic patent on streptomycin was licensed at the then *normal* royalty rate of 2.5% of sales. Since the research on streptomycin had been done in public facilities at Rutgers University, a higher license fee was thought to be unreasonable. However, an analysis of post-streptomycin prices reveals antibiotic price-unit cost ratios or "imputed" license fees of 80%. That is a 32 fold increase in royalty rates. Assuming constant unit costs and short run profit maximization in pre- and post-streptomycin situations, this change implies a decrease in the price elasticity of demand from 40 to 1.25 or an increase of price from 1.025 to five times unit costs.

Obviously, to openly change the license fees in the market for antibiotic bulkware from 2.5% to 80% of sales must have appeared exploitative to the general public. If however, the drug companies would integrate forward and alter their structure from a mere producer of bulkware to a supplier of final dosage forms, open market transactions would be transformed into hidden, internal transfer prices. Vertical forward integration had the further advantage that the supplier of the patented new drug would be able to directly address his advertisements to those who controlled the access to the patients: the prescribing physicians.

Thus a change in medical theory accompanied by the discovery of research and development as a method to exploit new medical insights altered the basic conditions for pricing new drugs, and stimulated a change in industry structure from vertical disintegration to complete vertical integration.

(3) The patient-doctor relationship can be seen as one between principal and agent. Yet the relationship is an imperfect one. Typically the patient is insured against the financial risks of sickness. This has the effect, called moral hazard, that a larger quantity of health care will be demanded at a higher price. The precise effects on quantity and on price elasticity depend on the specifics of the re-imbursement scheme. Moral hazard permeates the patient-doctor relationship. The patient has neither the knowledge nor the incentive to search for cost-minimizing treatments. Inefficiencies in the health services raise insurance fees. But this effect fails to signal the proper response because the individual insurance taker

is in a free rider situation. The doctor may or may not know the most efficient treatment. Since he does not pay, he has no incentive to search for it or to choose it. On the contrary, revenue maximization induces him to placate the patient's desire for care by supplying services of doubtful efficacy. The health insurance, which pays the bill, has little information on cost-effectiveness. And as long as it is protected by compulsory membership or other state-imposed restraints of competition, it has only weak incentives to enforce cost-effectiveness.

This short review of the problems of the supply of medicinal products is thought to be suggestive, rather than exhaustive or balanced. For the following argument it is irrelevant,

- (a) whether and to what extent "quality" regulation of drugs is necessary,
- (b) whether and to what extent a propensity to monopolize exists or is moderated by workable competition,
- (c) whether and to what extent the patient-doctor relationship is infected by problems of moral hazard.

It suffices to recognize that such fears found certain political expressions at certain points in time in certain member states of the Community. Each member state has found a unique response if not to unique questions, then at least to questions posed in a unique way.

Ever since its first pharmaceutical directive 65/65 EEC, the Commission has worked on the goal of achieving the mutual recognition of drugs in the sense that a particular drug authorized to be marketed by the competent authority in one member state would routinely be admitted by the authorities of the other member states. To achieve that goal the Commission has harmonized the whole drug review process from animal studies to clinical research on patients. Yet the harmonization of testing and review principles has not brought the routine mutual recognition. Quite to the contrary, national competent authorities routinely raise objections against each other's decision to authorize the marketing of drugs.

The reason is clear. Rules and principles have to be applied in the light of value *judgements* in matters of benefits and risks. Both are multi-dimensional concepts. A drug has a more or less wide range of effectiveness of curing, of treating symptoms, and of alleviating pain. Certain unwanted side-effects may be present in one and not in another group of patients. Judgements on acceptable risks are inherently subjective. How scientifically established aspects of a drug are valued depends upon opinions of medical schools, cultural traits of a country, and the extent to which social and economic policy considerations are imported into the regulatory decision of drug admission. Antibiotics, oral antidiabetics, neurological drugs, drugs against coronary diseases, even oral contraceptives show highly peculiar national characteristics of consumption. Social and economic considerations differ in their importance for the evaluation of the benefits and risks of a particular drug. In one country the decision of efficacy and safety is done on the

basis of comparing the new drug with already existing ones, in another country comparative judgements may not be allowed.

For reasons like these the Commission has failed in its efforts to achieve the mutual recognition of marketing authorizations. But even if the national competent authorities would mutually recognize their marketing authorizations, the fact remains that a new drug will not be uniformly available in all member states. The member states differ in their social security systems. Health insurance as such influences already the rate and direction of innovative activity in ways specific to the system. But imbedded in or parallel to social security countries practice various forms of price regulation and expenditure control in order to combat suspected monopolistic practices and moral hazard. These regulations determine whether and on what terms a drug which has been authorized to be marketed may actually be sold in a national market. Thus, each member state has to an important degree a unique set of institutional incentives for and constraints on choosing where to operate on the invention-innovation frontier of drugs.

What is the likely response of the Commission to this situation? Realizing that the mutual recognition does not and cannot follow upon the harmonization of testing and evaluation rules, the Commission will have to push for the installation of a common European Institution of Drug Admission (EIDA). A decision by EIDA would not, however, ensure that a new drug is uniformly available in all national drug markets. Different reimbursement schemes, price, profit, and expenditure regulations remain as barriers against the free movement of drugs. Eventually the Commission has to harmonize these regulations too.

Since that is a very distant step, what remains to be said about the next step of creating EIDA? Obviously, its institutional design will have far-reaching effects on the quality and the costs of the regulatory decisions. But what are the options for an institutional design, what are their effects on the regulatory process? This is not obvious! For possible answers we have to study the complexity of the regulatory task, the regulatory environment, and the organizational options of performing drug regulation.

A study of the organizational options for performing the regulation of drug development may start with a comparative evaluation of national drug regulation systems. Such an effort is beyond the scope of this paper. It is also not necessary for the reason that only two principles exist for such an organizational design: the agency solution on the one hand, and the *expert committee* solution on the other hand. The US Food and Drug Administration (FDA) is a much studied and well documented example of the first regulatory approach. The British *Committee on the Safety of Medicines* (CSM) is a typical representative of the other regulatory approach. Since its way of operation is less known, the following procedure is chosen. First, we study the general characteristics of the drug discovery process, in order to inform about the complexities of the

regulatory task. In a second step we study how the British approach to drug regulation has evolved as specific problems were identified and called for solutions. If we combine that information with what is already known about the operation of a FDA-type of regulatory system, we may be able to reach certain conclusions about the principles of organizing EIDA.

B. The Complexity of the Task of Regulating Drug Development

For every 1-2 "new chemical entities" (NCE) admitted to the market as a new drug some 10,000 chemical compounds are synthesized in the laboratory and *screened* for effects by administering them to isolated organs, to tissues, tumor cells, microbes, etc. Of the 10,000 NCEs some 1,000 look so promising that the initiation of animal toxicology studies seems justified. Because in the past certain drug disasters like the one involving *Elixir Sulfanilamide* <17> could have been avoided by simple animal tests, animal *toxicology* is seen as imperative before daring to further test a drug in *healthy humans*.

One of the first tasks in animal toxicology is the determination of that dose, measured by mg/kg weight of the body, which kills 50% of the animals. Besides this lethal dose LD₅₀ an effectivity dose ED₅₀ which has a success rate of 50% is measured. The quotient ED₅₀/LD₅₀ gives some very rough indication of the risk of giving the compound to humans <56;57>.

The next two steps in animal studies are what is called pharmacokinetics and *pharmacodynamics*. *Pharmacokinetics* deals with such questions as:

- * How is the substance distributed in the body?
- * How is the substance eliminated by the body?
- * Does the substance accumulate in some organs or e.g. in the bones?
- * What happens with the bioavailability of the compound if given by different routes and in different formulations?
- * How does the body transform - *metabolize* - the substance by its various physiological processes?

Pharmacodynamics is concerned with one of the most difficult tasks, namely the determination of how and why the compound works as measured by observable effects. Since only a few mechanisms of cause and effect have as yet been clarified, pharmacodynamics is a very uncertain part of drug research.

In regard to effectiveness in humans animal studies are highly unreliable models of evaluation<35;51;56;57>. This is especially true for the long-run animal studies which search for carcinogenic and mutagenic effects. Large variations may exist between different animals, but even

among some strains of the same animal; e.g. some strains of mice might develop breast cancer, while others do not. Toxicity results may lead to a wrong extrapolation about damages to certain organs. Animals vary widely in the way they metabolize substances, and humans may vary widely from animals. The antirheumatic effects of phenylbutazone could not be established in animals because they eliminate the substance in a few minutes, whereas man metabolizes only 15% per day. If Fleming would have tested penicillin on guinea pigs, probably the substance would never have seen the light as a wonder-drug, because it is a violent poison for them although not for mice. But penicillin is not a unique case. If judged by today's standards of animal studies, drugs like adrenalin, aspirin, cortisone, insulin, streptomycin, tetracycline, and numerous other ones would not be available, because they have highly detrimental effects during some phase of the animal studies.

Of the 1,000 NCEs on which animal toxicology had begun, ten survive and enter what is called phase I research. Here the drug is given to a small group of about ten healthy volunteers in order to study its pharmacokinetics. Phase I research is mainly concerned with safety aspects. What is the appropriate dose? What is a suitable formulation? How does it influence the bioavailability of the substance? Once the relative safety of the compound has been established, the pharmacodynamics, i.e. the efficacy of the prospective drug is detected during phase II research by giving it to a larger group of up to 100-200 patients. Having completed phase II the drug is taken over into phase III research on a still larger group of patients in order to search for possible adverse drug reactions (ADR) with and without taking the NCE in combination with other pharmaceuticals. During phase III research an application to admit the drug to the market will be filed <1;25;26;28;32;51;55>. Only 5% of all drugs entering phase III are not admitted to the market, whereas almost 30% of all drugs leaving animal toxicology do not survive beyond phase I, and close to 40% of all drugs leaving phase I do not survive beyond phase II. Thus, the knowledge gained during phase III on potential ADRs is apparently rather small <49>.

However, the chain of events stimulated by a drug may be very complex and may depend in various unknown ways on the specific situation of the patient or the patient-doctor relationship. Furthermore, unfounded claims tend to be made for all kinds of "patent medicines". Therefore, in 1954 Lasagna developed the concept of the *randomized, double-blind, controlled clinical trial* RCCT for founding an unbiased basis of drug evaluation. However attractive this test procedure looks in the eyes of the sceptic, it cannot be defended on a priori grounds to be the only valid test procedure. There must be room for choosing some other test design according to specific circumstances <32>.

Besides, the RCCT is not failure proof. Patient and doctor have a strong incentive to discover, what kind of drug, e.g. a placebo, they are using. If

the condition of a patient in a group selected for treatment by a less potent drug deteriorates, the physician may respond by giving additional care. Thus the comparative results may be biased.

While an ideal RCCT tells that a new drug is superior if given to a large GROUP of patients, it can say little about what it does to the individual patient in the everyday environment of the general practitioner GP. But, as has been shown by Lasagna too, for numerous reasons the naturalistic environment is the proper testing ground for a new drug. Hence phase II and III clinical studies, whether or not conducted on the basis of the RCCT, leave important questions on the safety and efficacy profile of a new drug unanswered. Research during the period of actually marketing the drug, phase IV, is left as the only way to collect information which is not readily appearing in relatively small groups of patients.

A first step in the direction of a post-marketing surveillance of drugs were post-marketing clinical studies. In 1970 Levadopa was admitted to the US market although not all clinical and toxicological studies had been completed, because people suffering from Parkinson's disease could be treated effectively for the first time. Some 1,500 patients were monitored for ADRs for a period of up to six years <31>. This drug admission procedure is called *monitored release*. But even such a large group of patients is too small to detect ADRs beyond the 0.1% level of likelihood of occurrence.

Also in 1970 a new beta-blocker - practolol - was admitted to the British market. It had fewer serious side-effects in the treatment of angina pectoris, high blood pressure, and disorders of heart rhythm. Therefore, it became the beta-blocker of first choice. After four years with an accumulated population of 200,000 users an ophthalmologist saw patients who complained about dry eyes. He heard that all were taking practolol. Upon reports to the company further investigations revealed that practolol leads to a very rare immunological reaction whose mechanism is unclear, but which necessitates eye surgery and leads to blindness occasionally <35, pp.79-81>.

Could such rare ADRs be detected ex ante during clinical phase II or III research? To better understand the situation, let us look at the risks of dying from certain illnesses or from other causes. The estimation of these risks tends to be highly imprecise. The confidence limits spans an order of magnitude. A particular event may, for instance, have the chance to occur in a group of 1 to <10, in a group of 10 to <100, or in a group of 100 to <1000 people. Correspondingly we may talk of risk levels 1, 2, or 3. This enumeration is unfortunate in that a lower risk level, e.g. 2 in comparison to 3, receives a higher number. But a risk level of one per thousand may be written as $1/1000$ or 1×10^{-3} . Therefore, I choose the notation "Risk Level -1" or "Risk Level -3".

Table 1: Comparative Risks of Mortality Caused by Illnesses and other Events

Risk Level RL i.e. one death per year among	Cause of Death by a Specific Illness or some other Event in:		
	General Population	Patients with a specific disease	Other Event
RL -1: 1 — <10	-----	Tetanus	-----
RL -2: 10 — <10 ²	-----	Cancer, Diabetes	Any
RL -3: 10 ² - <10 ³	Cancer, Coronary Disease	Arthritis	-----
RL -4: 10 ³ - <10 ⁴	Peptic Ulcer	-----	-----
RL -5: 10 ⁴ - <10 ⁵	Arthritis, Diabetes	Whooping Cough	Motor Car, Suicide
RL -6: 10 ⁵ - <10 ⁶	Pregnancy, Venereal Disease	-----	Railway, Homicide
RL -7: 10 ⁶ - <10 ⁷	Tetanus, Whooping Cough	-----	Falling Objects
RL -8: 10 ⁷ - <10 ⁸	Accute Rheumatic Fever	-----	Lightning

Source: Inman <19, pp.21-25>

The table says for instance: In a general population of ten to hundred thousand people one person will die either by suicide or by arthritis. But one person among one hundred to one thousand persons who actually suffer from arthritis is going to die from the disease. The ability to discover an ADR during phase III research lies around one percent. To test a new drug in a group of 100 - 200 patients requires a much larger overall sample size of patients, if the drug is tested against several other pharmaceuticals in a RCCT environment. As in the case of Levadopa risk level -3 may be reached by *monitored release*. To push the reasoning to some kind of extreme let us consider the introduction of a new drug against arthritis. By phase III research we are able to reach down to risk level -2. This does not exclude a lethal ADR in risk level -3. Assume both probabilities to die are the same with a chance of 1 in 1000. Assume further-more, a situation (1) in which the new drug does not heal but only alleviates the pains of arthritis, and a situation (2) where the drug cures arthritis with certainty. In the first case the patient's overall probability to die doubles from 1/1,000 to 2/1,000 or 1/500. In the second case the patient substitutes the risk to die from arthritis by the same risk to die while curing arthritis. In the first case the new drug becomes more acceptable the lower the risk level of the letal ADR. If the risk of dying from the ADR is not in level -3 but in -5, the overall risk of dying from arthritis and its treatment increases from 1/1,000 to 1/1,000 + 1/100,000, that is from 0.001 to 0.001001. That increase in overall risk appears bearable if the benefits from alleviating pain are reasonably large. The second case is obvious. A risk of 0.001 to die from arthritis is substituted against the risk of 0.00001 to die from the drug which cures the illness. Even if the drug has a probability to heal much lower than one, the benefit risk ratio is still tilted toward taking the drug. Assume that the

drug has a probability of 20% to cure arthritis. Then the patient has a risk of 0.8×0.001 to die from arthritis and a risk of 0.00001 to die from the ADR of the drug treatment. His total risk of drug treatment is 0.00081 which is by an order of magnitude lower than the no-treatment risk.

These purely illustrative calculations demonstrate that information on the relative frequencies of ADRs is vitally important for the estimation of reasonably accurate benefit-risk ratios of drugs. But here we confront a paradox of some kind. A serious illness, i.e. one in a mortality risk level of -2 or -3, requires reliable information on ADRs down to risk levels -4 or -5, whereas a less serious illness, i.e. one in mortality risk level -5, requires a much lower risk level for ADRs of -6 or -7. Since the sample size of patients required for achieving a lower risk level rises geometrically, the costs to establish a reliable benefit-risk ratio of a drug increase while the benefits of the drug decrease <23>.

Phase III research is no economical method to reach down to lower risk levels of drug treatment. If we would want to go down to risk level -4 we would need groups of up to 10,000 patients. This would be an unbearable burden on clinical investigators and on patients. It would also be prohibitively costly. Therefore, the discovery of rare ADRs can only be made and financed by actually selling the drug. This leads to *post-marketing surveillance* PMS as the other method of performing what is called phase IV research.

However PMS is not only a method to discover rare ADRs, it also helps to detect unexpected new indications of a drug. The following table lists a few examples of indications discovered by serendipity after their admission to the market:

Table 2: New Indications of Drugs Discovered Serendipitously

<i>Drug's generic name</i>	<i>New indication discovered</i>
phenytoin	anti-arrhythmic
lidocaine	anti-arrhythmic
probenicid	uricosuric
imipramine	anti-depressant
acetazolamide	glaucoma, epilepsy
thiazides	diabetes
diazepam	status epilepticus
propranolol	anti-hypertensive
vitamin D	hypoparathyroidism
trimethoprim	pneumocystis infectus
oestrogens, progestins	contraception
phenobarbital	epilepsy
iproniazid	melancholia
chlorpromazine	anti-schizophrenic
amphetamine	hyperkinesis
amantadine	anti-parkinson
metronidazole	rosacea

Source: Lasagna in <28;38>

Our provisional conclusions are: firstly, the discovery of drugs is a process with a very high degree of empiricism, that means, biomedical sciences have a low ability to predict the likely effects of new chemical entities on the inter- and intra-cellular physiological processes of the human body <25;35;51;56;57>. Secondly, to establish the benefits and the relatively frequent risks of a new drug candidate necessitates lengthy and costly animal studies and phase I to phase III research. These phases of drug discovery are densely regulated. What is the impact of regulation on the efficiency of the drug discovery process? Thirdly, any effort to estimate the benefit-risk ratio of a new drug depends critically on an effective system of post-marketing surveillance <21;22;39;40;43>. It is the contention of the following analysis, that in both respects the British system of drug regulation offers exemplary insights.

C. The British Approach to Control the Admission of New Drugs

1. On the History of Drug Control: From Henry VIII to Sir Derrick Dunlop <28;54;55>

The physician's concern about the quality of medicines is a secular one. Until a few decades ago the medicines were derived from plants, herbs, or like snake oil from animals. There were also "patent medicines" like unicorn horn, or eunuch fat. Adulteration of drugs was common. In 1540 Henry VIII promulgated a law against the adulteration of medicines and founded an inspectorate for the supervision of pharmacies. Other acts followed over the centuries. In 1858 the first statutory edition of the *British Pharmacopeia* laid the ground for a continuous standardization of quality control measures. In 1875 the first *Food and Drug Act* penalized the adulteration of drugs. But few effective drugs were available. Notable exceptions were morphine, known since antiquity, digitalis, discovered in the 18th century, and quinine for the treatment of "the fevers". Quinine was replaced by salicin, derived from the willow tree - *Salix* - growing in the swamps, where "the fevers" were thought to originate. Salicin led to the discovery of aspirin.

The number of effective drugs was not only limited to a mere handful, several of those few, especially the heavy metals mercury and bismuth were also highly hazardous. Syphilis, brought to Europe upon Columbus' return in 1493, was a common dreadful illness. Drer wrote from Venice:

"There is nothing that I fear more than the <<French sickness>>, everybody has it."

Drinking a kind of extract from a tree induced a high fever, the first hyperthermic treatment. But by 1529 Paracelsus had argued effectively,

although wrongly, against this treatment. "Ungentuum griseum", a mercury-porkfat salve, remained as the only slightly effective treatment. Its other substitute became the artificial infection with malaria. There was a chance that the high fever killed the spirochetes faster than the infected person. For centuries, therefore, the saying was valid:

"One night spent with Venus, and a lifetime with Mercury".

After the First World War organic arsenicals replaced mercury in the treatment of syphilis.. But an epidemic of jaundice and fatal hepatic necrosis among British soldiers treated for syphilis with organic arsenicals called forth the first report by the first Medical Research Council in British history in 1922.

But time was not ripe for a radically new approach to drug safety for the very reason that drug treatment was so inherently risky. The approach to drug safety remained a piece-meal one. A Dangerous Drug Act of 1920 was concerned with the problem of addiction. The introduction of insulin in 1922 raised problems of quality control. The 1930s saw the introduction of the first wonder-drugs against bacterial infections, the sulfonamides. Now a night could be spent with Venus, and gone were the horrific consequences of the love affair. After the sulfonamides came the antibiotics and the tranquilizers. Adverse drug reactions were observed, but they raised no fundamental concern in view of the hitherto unknown potency of the new generation of pharmaceuticals. In 1961 the medical community was jolted out of its sense of security by the thalidomide disaster. A special joint subcommittee established by the English and Scottish Medical Association recommended the foundation of an expert committee for the review of scientific evidence on new and old drugs. This led to the Committee on the Safety of Drugs CSD which started to work on January 1, 1964 under the chairmanship of Sir Derrick Dunlop. The CSD ceased its operation in September 1971, when its work was taken over by the Committee on the Safety of Medicines CSM. Sir Derrick's chairmanship has been hailed as a milestone in the development of an efficient drug control system.

Compliance with the decisions of the CSD was voluntary. The *Association of the British Pharmaceutical Industry* ABPI and of the *Proprietary Association of Great Britain* PAGB had promised that their members would seek advice on the conduct of toxicology and clinical tests, that they would submit the toxicity tests to the CSD before the initiation of clinical trials, whose results had to be presented to the CSD too, and that they would consult with the CSD in matters of warnings on ADRs and restrictions of a drug's use.

The CSD set up specific subcommittees which dealt with all problems of consultation and decision in a fast, informal, and unbureaucratic manner. The CSD put a major effort in the establishment of the *Yellow Card System* of post-marketing monitoring the drugs for ADRs. Under this system doctors are invited to use pre-paid, yellow cards for reporting any adverse reaction which they observe in conjunction with a drug to a

special subcommittee. In case the subcommittee finds sufficient supporting evidence special leaflets warn every physician. One of the first warnings concerned the risk of sudden deaths among young asthmatics using pressurized aerosols with sympathomimetic amines. Another case concerned reports that women taking oral contraceptives had a higher risk of thrombosis in unusual sites such as the veins of the face or the breasts. An analysis of the Yellow Card reports showed possible links to the dosage of the oestrogen, and eventually led to the recommendation of the Mini Pill as a solution to the problem.

The subcommittee which recommended the foundation of the CSD on a voluntary basis had also recommended to eventually turn to a legally binding system of drug regulation. One major reason was that the voluntary system reached only the members of the ABPI and the PAGB plus a few non-committed firms. The total number was about 600 companies. A white Paper on *Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines* of 1967 laid the ground for the Medicines Act of 1968.

2. Drug Regulation under the Medicines Act

2.1. Pre-Marketing Regulation of Drugs

Two years after its promulgation the Medicines Act became operative. A *Medicines Commission*, as of 1986 comprising 19 members selected from physicians, veterinary surgeons, chemists, pharmacists and from industry, was set up as an independent body. The routine administrative work is carried out by civil servants in the Medicines Division of the Department of Health and Social Security. The institutions have now been renamed the Medicines Control Agency (MCA) of the Department of Health DoH. Upon advice from the MCA the ministers of health and of agriculture appoint independent experts for a period of four years (renewable) as members of special subcommittees whose function is to advise the *Licensing Authority* in the MCA in its decisions on various aspects of drug regulation. In that respect three subcommittees are of special importance, namely

- * the *Committee on Safety of Medicines* (CSM),
- * the *Committee of the Review of Medicines* (CRM),
- * the *Committee on the British Pharmacopoeia*.

Each committee comprises 18-19 independent experts as members drawn from various specializations.

The Medicines Act introduced a licensing system for the introduction of all new and already existing drugs. All drugs which were sold prior to September 1, 1971 could receive a *licence of right* from the Licensing Authority. About 36,000 products were granted such licences. By now most of these products have been reviewed by the CRM for their efficacy

and relative safety. Products that pass the Licensing Authority after review and upon advice by the CSM or the CRM are granted *product licences*. They are issued for a duration of five years, renewal is possible.

In regard to the manufacture and sale of drugs specific licences have to be applied for. The MCA maintains an inspectorate for the control of quality standards.

The CSM advises on the admission of new drugs. To increase its degree of specialization while simultaneously preserving its operational workability, the CSM has founded subcommittees for certain tasks:

- * a subcommittee on chemistry and pharmacology,
- * a subcommittee on biological and antimicrobial substances,
- * a subcommittee on standards of herbal products,
- * a subcommittee on toxicology, clinical trials, and therapeutic efficacy,
- * a subcommittee on adverse drug reactions.

In Great Britain, and contrary to US procedure, the drug manufacturer is permitted to pursue his development of a NCE until he has completed the tests in healthy volunteers. Before he begins tests on patients he has to obtain a *Clinical Trial Certificate* (CTC) from the MCA which is based on the full documentation of the test results of the animal studies and the ones on healthy volunteers. However for about eight years most in-patient-studies are now conducted under clinical trial exemption certificates (CTX). This procedure has been introduced in order to speed up the regulatory decision making and in order to prevent a shift of clinical research from Great Britain to foreign countries. Under the CTX procedure the MCA receives a summary report of the full documentation of the test results, and if the agency does not object within 35 days (an extension of 28 days is possible), the company is automatically allowed to begin with the clinical studies in patients.

The CSM does not consider ethical questions of clinical trials. These are dealt with separately by ethics committees formed by hospitals on a regional basis. If all trials have been completed, the company may apply for a product licence. The subcommittee responsible for the evaluation of the application, e.g. the CSM or the CRM advises the Licensing Authority. If it is unable to advise the issue of a licence, the applicant is given the opportunity to respond to the opinion of the Committee in an oral hearing or in written comments by presenting new arguments, evidence, or by modifying the application. The Committee reconsiders its opinion in the light of the representations of the applicant. If the Committee remains unconvinced, it may render the advice of a flat refusal of a licence. However, such a procedure is most unlikely. Usually the Committee decides "to provisionally not advise" the issue of a licence, and gives the applicant a second chance to respond. If the applicant fails to convince the Committee of its position, he may apply to the MCA as the final resort of appeal during the advisory procedure.

The Licensing Authority is not bound by the opinion of the CSM or by an appeal opinion of the MCA. Yet in matters of safety, efficacy, and

quality the Authority has to reconsult the CSM or the MCA, if it disregards their opinion. The applicant for a product licence can appeal to the High Court of England (Court of Session in Scotland) for a review of the decision of the Licensing Authority in matters of law.

2.2. The Post-Marketing Surveillance of Drugs

Several approaches to post-marketing surveillance coexist in Great Britain <3;4;18;19;20;21;22;23;24;31;40;43;45>. They are more complementary than competitive. A basic methodological distinction should be made between observational and interventionist studies. The former collects data after the therapeutic decision has been made. The latter is a clinical trial.

The CSM inherited the Yellow Card System from the CSD. The system is operated by the MCA of the DoH under the advice of the CSM's subcommittee on adverse drug reactions. All prescribing doctors receive pre-paid yellow cards and are invited to report all serious or unusual reactions to drugs, be they old drugs or new ones. Some 16,000 cards per year are returned. Roughly half of them are mailed by GPs, 35% come in from hospitals, and the rest from sources like dental surgeons or coroners. The MCA has a number of full-time, in-house physicians who discuss all incoming reports, follow-up reported events for possible links to the literature, communicate with the reporting doctor for further information, and may seek the contact and advice of some 200 part-time collaborating medical field workers.

The Yellow Card System missed the rare adverse drug reaction of practolol, but it had success like the detection of the thromboembolic risk of oral contraceptives. It is an imperfect system. First, there is a tendency to underreport observed events. It is estimated that only 10% of the observed drug related events are reported. Second, the Yellow Card System gives only anecdotal evidence in the sense that it is unable to give data on the absolute number of drug treatments. Hence it lacks the denominator as a basis to calculate the relative frequency with which a drug related event occurs.

The tendency of underreporting has several reasons. An almost unsurmountable problem is given by the task

- a) to define an adverse drug reaction in an operational way, and
- b) to discern when an adverse drug reaction is present.

Given that patients tend to be in a situation which is therapeutically unique to some extent, how is it possible to distinguish an *adverse event* occurring during the treatment from an *adverse reaction* caused by a specific drug? This problem is especially serious when drugs are given against life-threatening malignancies for the very reason that these drugs are almost always highly toxic. Other reasons are related to the fact that doctors are failing human beings too, e.g. fearing to be accused of negligence or malpractice, if they report an ADR.

To overcome problems like these another surveillance system had been founded in 1980. It is called *Prescription Event Monitoring* - PEM - and is operated by the *Drug Safety Research Unit* DSRU at the University of Southampton. Its founder and current director Professor W.H.W. Inman had previously worked to establish the Yellow Card System. How PEM operates is best described by reporting on PEM's first pilot study of the anti-arthritic drug benoxaprofen or Opren <18;19;20>.

DRSU asked the *Prescription Pricing Authority* PPA, which collects all prescriptions written for the National Health Service in order to remunerate the pharmacists, to identify all prescriptions for Opren written since January 1, 1981. The prescriptions identify the doctor and the patient. For the pilot study 6,000 patients were chosen. On January 1, 1982 Green Cards were sent to their doctors that inquired about any unusual event observed during the past twelve months. The doctor is not asked to make any inference about drug related causes and effects, he simply reports the events that he has stored in his records anyhow. Upon return of the Green Cards eight cases of jaundice were discovered. Because by now DSRU knew both the names of the patient and of his doctor, these discoveries were followed up. It turned out that five of the eight cases were unrelated to the drug. By that time some further 18,000 patients had been included in the study expanding the number of kidney or liver failures by 46 cases. 48 of the total of 54 cases could be followed up successfully. In those 48 cases only a single one could be related to Opren with a high degree of confidence. In five other cases Opren could not be ruled out as a probable cause. Adding the six cases which could not be investigated to the probable cases, the record for the ADR "liver or kidney failure" among a total population of 24,000 patients was the following:

- * one patient whose ADR was almost certainly caused by Opren, but he recovered after stopping the treatment with the drug,

- * and eleven patients whose ADR might have been caused by Opren.

In the meantime it had also been discovered that the dose of 600 mg per day was too high, because the drug had a long life-time. It was especially hazardous for elderly patients of the age of 70 and more. Yet about 40% of all patients receiving Opren were in that age group. Consequently that group could be expected to show larger incidences of kidney or liver failure. Reduction of the daily dose would have been the appropriate response. Yet, the discovery came too late. On May 8, 1982 the British Medical Journal published a note, where a doctor reported that all six patients that he ever treated with Opren had died. This anecdotal evidence sufficed to push the CSM and the Licensing Authority to revoke the product licence in July 1982.

Although PEM's results came too late to prevent a panic decision, the episode demonstrates how PEM can be used both pro- and retrospectively to study a given drug in a sample population of 20,000 patients. About 70% of all GPs in England participate voluntarily. In most projects four

drugs are evaluated simultaneously; each physician receives four Green Cards per drug in order to keep the burden of cooperation in narrow bounds. A response rate of 70% of all GPs is already high on its own terms. But it is still higher in view of the fact that 10% of the cases are lost, because patients move out of England to other parts of Great Britain, 5% of the cases are lost because doctors have retired. Hence only 15% of the cases could be related to some kind of unwillingness to cooperate. Yet that percentage may result from the fact that these doctors are engaged in investigational studies for drug companies.

PEM is limited in its coverage to England. In Scotland, Wales, and Northern Ireland the correct identification of a patient from the prescriptions is extremely difficult for a very simple reason <23>: The inhabitants share a very limited number of the same names. However, in the Tayside area of Scotland a *Medicines Evaluation and Monitoring Group* Memo has been set up at the Department of Clinical Pharmacology of Dundee University <3;4>. In Tayside each resident has a unique Community Health Number (CHNo) which reflects his age and sex and is related to his hospital records which are kept in a computerized form. The area has some 400,000 residents. This system of record linkage has been used to study the post-marketing profile of cimetidine.

Medical Record linkage systems like Memo seem to be a case of first choice in highly centralized health care systems provided that each patient is identifiable by a unique number, that diagnoses are collected reliably on a standardized basis, and provided finally that the confidentiality of the records is guarded beyond any doubt. However, the higher the degree of centralization in a system of record linkage, the larger the problem to safeguard confidentiality. Furthermore, the overall size of the system must be very large, if drug surveillance aims at low risk levels. Record linkage in Tayside with 400,000 residents found 3802 persons, who took the drug cimetidine between August 1980 and April 1981. The size of that group does not permit to reach beyond risk level -3. Especially in the case of new drugs it is important to rapidly achieve large sample sizes of drug takers. In this respect PEM with its 50 millions of England's inhabitants as a data base is a much more economical system of record linkage. A system like Memo incurs the high costs of linking all medical records irrespective of any preformulated question. PEM incurs but the marginally low costs of linking records on a selective, ad hoc basis in view of a specific question.

Memo is a comprehensive system of record linkage, whereas PEM is an event-related linkage system. Both systems have specific advantages which make them complementary rather than competitive. The comprehensive linkage of medical records makes it possible to study a drug over a long period of time against variously formed control groups. Usually there exists already some kind of alert or suspicion that the drug may cause some event. The alert may come from pre- or from postmarketing observations. Comprehensive record linkage permits a kind

of post-marketing clinical evaluation of a drug. It may be used for abbreviating preclinical phase III research by the early monitored release of a drug. This abbreviation is especially valuable for serious diseases and drugs with high, life-saving benefits and a correspondingly high level of acceptable risks. Comprehensive record linkage has also a comparative advantage in evaluating drugs used intermittently during short intervals. However, in situations of rarely occurring drug-related events and lower levels of acceptable risks the comprehensive linkage of all medical records is an uneconomical approach. It is speedier and far less costly to use the PEM method and to link the medical records in respect to a specific drug or a particular group of drugs. This can be done retrospectively for already existing drugs and concurrently for newly introduced drugs.

A well functioning PEM-surveillance helps to turn a major weakness of a spontaneous ADR-reporting scheme like the Yellow Card System into a major strength. If doctors would report all drug-related observations routinely, the system would be overburdened by too much "statistical noise". If, however, the reporting of events on a broad scale is economized by the PEM method, spontaneous reporting can be reserved to the very unusual drug related observations. This raises the probability that even very rarely occurring adverse (or beneficial) drug reactions will be discovered relatively early during marketing.

In view of the fact that the company which has researched and is marketing a drug has in-depth information on the drug and is continuously up-dating it through its own information system, general PMS-systems ought to cooperate closely with the drug companies. In the United States the FDA receives the preponderant share of its information on ADRs from the drug companies.

Recently there have been efforts to create a new market for the medical records of the GPs. With the tendency to computerize the clerical work of general practices software suppliers have realized that the medical records represent a wealth of information for the drug companies provided the records could be linked in a standardized form. Companies selling computer systems to GPs offer the systems free of charge if the GPs in turn agree to link their records to the system. IMS too is starting to capitalize on the record linkage of GPs. It remunerates GPs for their willingness to cooperate in what it calls Drug Event Monitoring System Demos, and sells the evaluation to the drug companies. The trend to commercialize the patients' medical records has its own by-product distortions <23>.

First, record linkage has the highest value to the drug company, if it can be used to generate observations on a specific drug promotion. The major advantage of prescription event monitoring is its ex post factum nature. The doctor reports his observations uninfluenced by the knowledge that somebody might be interested in his observations. In a promotional study he is paid for supplying observations on a specific drug. Thus, his therapeutic decision is influenced by the commercial value

of the drug observations which he supplies. He is induced to change his therapy in response to the drug observation. In that situation it is most likely that the physician chooses to treat less risky patients, so that the final evaluation of the data overestimates the relative safety of the drug.

Second, if commercialized record linkage is used in promotional studies of new drug introductions more time elapses after which the first non-distorted observations on a large scale become available. Finally, even if the willingness of doctors to cooperate with drug event alerting schemes remains unaffected, his ability to cooperate is reduced by the increased effort demanded by record linkage. Thus, the ability to detect ADRs relatively early by Yellow or Green Cards suffers the more widespread commercialized record linkage becomes.

The probability increases that a major drug disaster occurs. To avoid it the commercialization of general practice record linkage ought to be regulated by the subcommittee on adverse drug reactions. Regulation by the subcommittee is not understood in a close, day to day supervision of its operation. No individual PMS system is an efficient solution to all problems of drug surveillance. Memo, PEM, and Yellow Cards have their specific comparative advantages. A commercialized linkage of general practice medical records, if properly executed and linked to programs like Memo or PEM, may be of value both to GPs, drug companies and to drug surveillance. What is important is that the various drug surveillance systems are operated under the respect of the principles of their mutual complementarity.

D.Principles of a Common European Approach to the Regulation of Drug Development

1. The Decentralization of the Systems of Post-Marketing Drug Monitoring

The free movement of drugs in the European Community is not only hindered by the fact that the national competent authorities render different value judgements on the merits of therapeutic approaches and on issues of relative benefits and risks of drugs. On top of these drug-specific differences come *health-policy-specific* differences in the operation of the social security system, and *industry-specific* differences in the control of the drug industry's prices and profits, and differences in the extent to which national governments assist their national drug industry by more or less hidden protectionist devices.

A common European approach to deal with drug-specific issues is, therefore, only a first step toward to free movement of drugs in the Community. A new drug may be "authorized" to be marketed community-wide, yet this fact does not ensure that the pattern of drug use

is uniform throughout the Economic Community. First of all, drug-specific reservations towards a drug's use will persist in the national medical communities despite the fact that a central European institution like EIDA has given one set of value judgements where previously a multiplicity of sets of value judgements had been given. A German doctor, for instance, will use a new antibiotic more restrictively and a new oral antidiabetic less restrictively than his British colleague. Only in the long-run may the work of EIDA erode such differences. Second, even when no drug-specific differences of drug use exist, health policy and industry specific national measures may still create discriminatory conditions of availability. Consequently, a uniform community-wide marketing authorization will not result in a uniform pattern of drug use.

That means that the observed ADR profile of a drug is likely to vary from country to country. Aplastic anaemia has been related to chloramphenicol in Great Britain or Belgium, but not in Germany. Pulmonary hypersensitivity upon taking nitrofurantoin has been reported in Finland and Sweden, but not in Germany, Great Britain, or Holland. SMON as a reaction to clioquinol seems to be limited to Japan. Hence, there may also be population-specific patterns of adverse drug reactions. Population-specific covers a wide range of racial, genetic, dietetic aspects and culturally, socially, and economically determined ways of behaviour.

If the ADR profile of a drug may be country-specific, it is a matter of principle that the system for reporting and analyzing the ADR profile has to be country-specific too. Yet this is also a question of organizational expediency. The study of the British approach to post-marketing surveillance demonstrated that the range of possible solutions to the discovery of ADRs critically depends upon the institutional characteristics of the health care service. A system like PEM would not work outside of the environment of the British National Health Service, whereas a spontaneous reporting scheme like the Yellow Card System can be and has been realized in most countries. Nevertheless even spontaneous reporting schemes may differ in their mode of operation. In the USA, for instance, most (85%) spontaneous reports on drugs come from drug companies, in Great Britain most (85%) come from doctors.

Because each member state of the Community has a health care system which is sui generis to a large degree, each member state should have the freedom to develop its own solution to the post-marketing evaluation of drugs. Each member state needs a spontaneous reporting scheme. Yet beyond that requirement a wide latitude of approaches is feasible. Countries with a decentralized health care system may find it more appropriate to rely on post-marketing clinical studies using cohorts of linked medical records. Countries with a centralized health care system may try to follow the British approach to rely more on post-marketing surveillance proper. Great Britain is a model case, in that it demonstrates that the Yellow Card System is run by the DOH, i.e. by the government, whereas PEM and Memo are university associated, independent systems

operating along different conceptual lines. Despite this diversity of approaches in conceptual and institutional design, close cooperation in post-marketing monitoring is achieved. The freedom to develop country-specific solutions to the drug monitoring task increases the degree of search and experimentation, thus widens the choice set from which to borrow concepts and approaches.

Although the national competent authorities should retain the overall responsibility for the post-marketing drug monitoring, it would be preferable if EIDA would coordinate the community-wide cooperation of the monitoring systems. At present, for instance, PEM offers unique possibilities to perform in-depth studies of ADR profiles down to very low risk levels. Why should such a capability not be used to investigate spontaneous reports of suspected ADRs received in Spain, or why should it not be used to study the ADR profile of a drug which originated in France? If EIDA could assure itself that the national monitoring systems would cooperate closely some important results would follow.

Firstly, the drug discovery process is highly empirical in character. Neither the potential range of adverse, nor that of beneficial drug reactions is to be discerned by pre-market observations to a high degree of certainty. Post-marketing monitoring is not only essential for establishing the benefit-risk ratio of a drug, thus making its use more rational and efficient, it is also a drug-discovery method by itself. What is considered to be the beneficial and the adverse effect of a substance may change over time as more is learnt about it. The effect of a sulfonamide compound to lower the level of blood sugar is an adverse effect, if the primary use is seen in its bacteriostatic properties. However, that same effect becomes the therapeutic one, if the substance is developed into an oral antidiabetic. Thus, a highly performing system of post-marketing drug monitoring is

- (a) a contribution to increasing the efficiency of drug therapy,
- (b) a method to search for new indications of existing drugs, and
- (c) a method to discover completely new kinds of drugs.

Secondly, the overall level of relative drug safety is to a considerable degree the result of a trade-off between the extent of the pre-marketing and the post-marketing evaluation of a drug. This has neatly been brought out by the former FDA-commissioner Alexander Schmidt in his famous "equation" determining the level of drug safety <30, p.16>:

$$\begin{array}{ccccccc} \text{Information} & & \text{Ability to get} & & \text{Ability to} & & \text{Ease of} \\ \text{needed to} & + & \text{information} & + & \text{control use} & + & \text{withdrawal of} \\ \text{approve} & & \text{after marketing} & & \text{after marketing} & & \text{drug approval} \\ & & & & & & = C \end{array}$$

The first two elements of the equation state that any constant level of drug safety C results from a combined effort of pre- and post-marketing drug study. Thus, if the national competent authorities use the full potential of the diversity of approaches to post-marketing drug monitoring, in no other part of the world does such a rich potential exist, then EIDA has

more options to search for ways to lower the ever increasing demand for more animal and clinical studies. In comparison to other world markets the European Community would have a unique capability to limit the increase both in time and in costs of developing new drugs. This increases the comparative advantage of the European drug industry.

Thirdly, a decentralized approach to post-marketing monitoring reduces the likelihood of panic decisions. Experience has shown that the general public has an irrational attitude towards drug-related risks. In the case of oral contraceptives it had been established that the risk of a young, healthy woman to die from thrombosis is eight times higher, if she takes the pill. What a tremendous increase of risk! However, with a ratio of one per 100,000 per year the risk of dying from thrombosis after taking the pill is ten times smaller than the risk of committing suicide, maybe because of an unintended pregnancy. And what about the risk of dying from pregnancy for other reasons? It is this kind of irrationality towards drugs which forces even competent authorities to render panic decisions, Opren is a case in point. Panic decisions "protect" by denying a treatment without asking for the costs of such a denial in terms of pains alleviated and lives saved. A decentralized institutional design of the post-marketing of drug monitoring is a shield against panic decisions. A certain drug may have a country specific incidence of an ADR. It is then up to the national competent authority to weigh the evidence and to take the appropriate measures. A central European agency would find it very difficult to defend a nation-specific decision. Should the drug-related event be a fatal one, the pressure by the general public to revoke the product licence for the whole Community becomes almost irresistible. Thus a decentralized, nation-specific monitoring of drug events reduces the industry's risk of unjustified product recalls and protects the patients' genuine interest in an adequate drug therapy.

2. The Centralization of the Regulation of Pre-Marketing Drug Development as a Problem of Institutional Design

The experience with the mutual recognition and concertation procedures under EC directives proves one point beyond any doubt. The community-wide centralization of the regulation of the drug development process up to the decision on the marketing authorization is the precondition for an eventual free movement of medicinal products in the European Community. There has to be founded a European Institution for Drug Admission (EIDA). But by relying on different organizational principles, EIDA can be shaped into two opposing directions. Following the approach of the United States and several European countries EIDA may be realized in the form of a European Drug Agency (EDA). Adhering to British traditions EIDA may become a European Committee on the Safety of Medicines (ECSM). Which way should be chosen? The answer has to be given in reference to the political environment in which the regulation

of drug development takes place, and in reference to the problems of the regulatory task.

2.1. The Political Environment of Drug Regulation

The general public is an important part of the regulatory environment. Mistrust, emotionalization and a tendency to uninformed value judgements are the main characteristics of the public's attitude toward the drug industry. Ever since Senator Kefauver launched his hearings on the drug industry, the public has heard of sensational reports on monopolistic prices, on unfounded claims of drug efficacy and safety, and on trivial innovations advertised as breakthroughs in therapy. Parliamentary investigations, monopoly commission reports, court trials under anti-cartel laws, studies by consumer protection associations, all have added pieces of evidence, fancy and folklore to the public image of the drug industry. The more the representatives of the drug industry and other observers know that this image is distorted, the more important the public's attitude becomes as a problem of public policy design.

First, the public demands protection and security against faulty claims and dangerous medicinal products. Second, the drug industry has neither the capability to ensure that no cases of misconduct will occur, nor has it the credibility that it would do so, if it were able to. Third, the public is quite uninformed about drugs, how they work, what their benefits, what their relative risks are. Most people have at best only a very vague realization of Paracelsus' dictum, that drugs are useful poisons. For these reasons EIDA has to be credible in both directions (a) towards the general public and (b) towards the drug industry. It should avoid being drawn into the adversarial relationship which exists between the public and the industry.

2.2. The Problems of the Regulatory Task

An all-important problem of the regulatory task is given by the high degree of empiricism of the drug discovery and development process. Where theory has a low capability to predict what can reasonably be expected to follow from a set of conditions the "art of muddling through" is a sensible scientific approach. In reference to drug regulation it is not called "muddling through" but "flexible and pragmatic". Yet the demand on the regulator is the same. Being flexible and pragmatic does not imply being without principles. It simply means that the regulator is keenly aware of the limitations of established principles. A scientific rule, well founded in past experience, may imperceptively become an unfounded article of faith or scientific dogma.

Animal studies have been highly useful in the past in avoiding drug disasters and in gaining pharmacokinetic and pharmacodynamic insights. Yet, on the other hand, animals are unreliable models of the response of

humans. Furthermore, the demands on animal studies have risen to the point where the sacrifice of hecatombs of animals become ethically undefensible. Animal studies are a central issue in the judgement on how to conduct the discovery of drugs.

In the United States no tests in healthy volunteers may be performed without the prior permission by the FDA. Animal studies are a vital input into the decision whether or not to allow the tests in healthy humans. In Great Britain the testing on healthy humans can be performed without the prior permission of the CSM. It has to issue a Clinical Trial Certificate (CTC) before tests in patients begin. Clearly the US approach puts more emphasis on animals as *reliable* models of drug evaluation than the British. Furthermore, the CTX clarification is given by the CSM almost routinely, provided that there is reasonable confidence in the scientific standard of conducting the trials in patients. The CSM does not consider ethical questions. These are left to the responsibility of local ethics committees. Thus an institution like EIDA has to exert judgements on issues of testing in humans after or prior to a CTC clearance and on the density of supervising clinical trials, ethical questions included or excluded.

The next step, where serious issues of judgement have to be decided, starts with the process of evaluating the documentary evidence submitted with the marketing application. The requirements on the collection of the documentary evidence have been standardized by EC directives and are not below US standards. But important value judgements have to be exercised in each individual application. To what extent should evidence gained by double-blind randomized clinical trials be required? That requirement may raise highly controversial ethical questions in specific situations. To what extent is it preferable to test the drug in a statistically less demanding context? Or may it be better to test it mostly in the naturalistic environment of post-marketing surveillance? How is the benefit risk profile of a drug to be evaluated? And finally, the regulatory authority has to answer how much responsibility it wants to delegate to the doctor and his patient to decide what risks are acceptable to them.

Looking over this list of questions two conclusions follow. First, the questions concern issues where medical and related expertise are required to sharply focus each issue. However, the answer belongs to one of two kinds. Either the issue is one where scientists may disagree on reasonable scientific grounds. Or the issue concerns a plain value judgement. Second, the questions originate at highly critical steps in the drug innovation process. Examples are: When to go from animal studies to those in humans? Is a trial certificate required? How much evidence on animals is requested, if a certificate is required? How closely are trials in patients to be monitored? How much freedom is left for the design of the trials? How is the trade-off between pre- and post-marketing drug monitoring decided? How much responsibility ought to be left to the patient and his doctor to decide in their individual situation what risk they find

acceptable? How these questions are posed, and how they are answered is obviously vitally important for the performance of the drug innovation process.

3.The Problem of the Design of a European Institution of Drug Admission (EIDA)

With the profiles of the problems posed by the political environment and by the regulatory task itself as a background we compare the two institutional options, the agency solution EDA on the one hand with the expert committee solution ECSM on the other.

In whatever form EIDA would be realized a major problem is to gain credibility in both directions, that is with the general public and its political representatives and with the drug industry and the medical community. Public Regulation is a typical US American institution. The US evidence shows that regulatory bodies do not escape a severe accusation <15;27;41;46;>:

Although they have been founded in order to control the industry in the Public Interest, they have been captured by the industry to "control" it in the industry's interest.

The US FDA is no exception. Consumer groups, Naider's Raiders, congressional members and committees are always ready to suspect that the FDA gives in to industry pressure. In the past there have been periods when year after year between 35 and 40 congressional hearings had been held on the FDA. Anyone who has read the transcripts knows that the atmosphere tended to be chilly, and that the burden of labour put on the agency staff for the preparation of defences was enormous.

One particularly drastic case involved the admission of the beta-blocker propranolol for the treatment of angina pectoris to the US market in 1974. By that time the drug had already become the standard treatment for angina in Great Britain, where it was considered to be a major breakthrough against hypertension, an indication not permitted in the United States. Why this delay of a drug which had already become the standard treatment outside of the USA? There were suspicions that certain strains of mice developed cancer! But how much weight is to be given to such a suspicion in view of the fact that the suffering patients had a low life expectancy anyhow, and the only alternative were open heart surgery? However, the FDA stood under very severe congressional criticism for its decision to admit propranolol for the indication of angina. From March until October 1974 it had to defend itself before the Subcommittee on Intergovernmental Relations, the Senate Committee on Government Operations, and the Senate Health Subcommittee. Lasagna and Wardell qualify these congressional interventions as follows:

"The continuing congressional criticism of the final approval of beta-blockers for angina is destined to become a classic in the history of political pharmacology, with very wide implications for the legislation

and regulation of drugs. It is hard to believe that an advisory committee was still debating the approval of this drug for angina when a physician's failure to use this drug - for instance as a trial in most patients prior to coronary artery surgery - would be regarded, if not as malpractice, then certainly as substantially suboptimal medical practice" (original emphasis) <53, p.122>.

Although the fate of the FDA is to some extent uniquely American, it is certain that an EDA would not escape similar pressures of *political pharmacology*. Maybe the pressures would be less visible and more subtle, yet they would be exercised. But political pharmacology destroys the fundamentals of credibility in all directions. Every report on political pressures reinforces the public's conviction that EDA is deficient in the exercise of its duties. Political pressures may become a provocation of the expertise of the medical community, and they certainly will be received inimically by the drug industry. An agency, therefore, has to protect itself against the potential of universal distrust by taking appropriate safeguards.

Firstly, it must insist on formal and well documented procedures and on avoiding informal encounters. Secondly, an agency has a built-in tendency to favor pre-marketing evidence on drug efficacy and safety over post-marketing evidence. Any negative piece of evidence gained after the drug has been authorized to be marketed may be used to accuse it of negligence or of a pro-industry bias. Since only negative evidence will be noticed, the positive one is taken for granted, the agency has to assure itself by pre-marketing investigations that the likelihood of negative post-marketing evidence is kept to a minimum. In case some piece of negative evidence turns up during a drug's use, it is imperative that the agency is able to prove that it has adhered strictly to the standard procedures of conducting animal and clinical studies. The agency has a tendency to be dogmatic in regard to drug testing procedures. This explains the fact that new test procedures rarely replace older ones; in most cases new tests, especially during animal investigations are just added on to the old ones. A third result follows. The true benefit risk ratio of a drug cannot be established for lower risk levels by using the normal rules on sample sizes of patient groups. An agency, therefore, has the incentive to ask for an increase of the sample sizes during clinical research. Again, the strict adherence to standard protocols protects against the accusation of negligence. Thus, not only the choice of sample sizes but also the formation of patient groups is biased by the agency's risk aversion against political pharmacology. It is always safer to add another kind of control group. Fourthly, it becomes apparent that the agency is forced by the ever present threat of political pharmacology to try to oversee the whole drug discovery and development process as close as possible. In this respect it is only consequential that the FDA regulates the testing of drugs in healthy volunteers and that it closely oversees the design of patient clinical studies. Fifthly, the agency suffers from problems of recruiting appropriately

qualified staff. A scientist joining a drug agency discovers that the procedures have to be bureaucratic. He has little chance to contact members of the outside scientific community informally on problems of regulatory control. On the one hand he has to be so well qualified that he is able to evaluate research results from the frontiers of science, on the other hand he has to be resigned to live in a bureaucratic environment far away from the frontiers of knowledge. Over the years the stock of his scientific expertise becomes obsolete. The agency expert tends to have low credentials.

A comparison between this set of behavioral incentives and the profile of the requirements of the regulatory task reveals a striking contradiction. The regulator is called upon to be keenly aware of the limitations of medical theory and pharmacology to predict and to explain the effects of chemical compounds. He must be open to surprises and to untried methods. His conceptual grasp of the nature of the innovation process must be a "high surprise model". Yet the constraints on the regulatory agency force the regulator to act, as if the drug discovery and development process were adequately portrayed by a "low surprise model". The regulator has to act on the basis of a wrong model of innovation. The forces of cognitive dissonance (or consonance) assure that in the long-run the agency will be staffed by people adhering to the "low surprise model" of the innovation of drugs.

Decisions on the basis of the wrong model of innovation have obvious consequences. This can be proved by referring to evidence of the work of the FDA <6;7;13;14;25;26;28;37;39;52;53>. When the regulatory requirements of the Kefauver Amendment were introduced, the United States experienced a very substantial drug-lag. In comparison to European countries, especially Great Britain, important new drugs were retarded in their introduction to the United States. A pharmacologist wrote in 1975:

"It is obvious to every English-speaking medical student outside the United States who buys an American textbook of pharmacology or medicine, only to find that the sections on current drugs on therapeutics are so out of date that he has to buy a British textbook as well...American textbooks are so hopelessly out of date when used abroad as to be often irrelevant" <52, p.165>.

In the same volume it was also reported that Great Britain has almost twice as many new drug introductions than the United States which previously was the country leading in new drug introductions. Consequently, the choice of the wrong model of innovation has reduced the rate of new drug discovery and the availability of advances in drug therapy. It must be added, that in the meantime the FDA has worked hard to make its regulatory process more efficient. However, it did so only grudgingly. And without the hard evidence from Great Britain, that is from a country with a different approach to drug regulation, there would have been no opportunity to discover these deficiencies. It is,

therefore, of overriding importance that the British, the expert committee approach to drug regulation is taken.

It starts with a select committee of the European Parliament which chooses outside members of a *European Medical Control Agency* (EMCA) from various specializations like medicine, pharmacology, chemistry, industry, etc., two for each country. The European Commission nominates in consultation with the EMCA members of European Subcommittees, e.g. on the Safety of Medicines, and on a European Pharmacopeia. The members, two for each country, are again drawn from various specializations. The Subcommittees like the ECSM specialize by forming subcommittees of their own. The ECSM, for instance, establishes subcommittees on

- * chemistry and pharmacology,
- * biotechnology,
- * herbal products,
- * toxicology, clinical trials, and therapeutic efficacy,
- * adverse drug reactions.

The European Commission establishes a European Drug Agency (EDA) with a Licensing Authority. EDA handles the clerical and administrative work for committees like the ECSM and the respective subcommittees. The Licensing Authority of EDA is not bound by decisions of the ECSM. However, it has to re-consult the ECSM, if it deviates from its opinion. The European Medical Control Agency is the board of appeals in all cases decided by the Licensing Authority.

This approach to drug regulation transforms EIDA into a hybrid form of organization. On the one side, there is a central bureaucracy and a central competent authority for new drug applications. On the other side, expert committees act as intermediates in the decision making process and on the board of appeals. Outside experts are much more independent in their career than inside employees. In comparison to a central agency a committee of experts is more diffuse in its operation. It is, therefore, politically more difficult to attack an expert committee than a central agency. Expert committees tend to be formed of the eminent representatives of the various sciences. They ensure that the regulatory work is closely attached to the frontier of knowledge. This lends them a higher degree of credibility. Because of their scientific prestige and their political independence expert committees shield the European Drug Agency against efforts of political pharmacology. The British CSM does operate informally, it does grant hearings in cases of dispute, where the FDA has to insist on written representations. Informality is vitally important in situations of uncertainty. The researcher may observe certain unexpected abnormalities in some species of animals or during in-patient studies. Should he report to the regulator? In a formal procedure he risks that the whole development process will be stopped. Thus, he opts not to report the observation. The committee offers the opportunity to discuss doubtful observations in a detached, informal environment. The discovery

and development of drugs is a process of sequential decision making on a pathway characterized by a high degree of empiricism. At several points of this pathway critically important enlightened judgements on matters of test design, weighing of evidence, trade-offs between different values, etc. have to be made. An expert committee has both a higher degree of enlightenment and a larger ability to act accordingly. It works according to the "high surprise model" of drug innovation. Thus the European Institution of Drug Admission is appropriately realized by creating

*a European Drug Agency EDA as the Licensing Authority which cooperates with

*a European Committee on the Safety of Medicines ECSM under the authority of

*a European Medical Control Agency EMCA.

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