

**SOME INTERNAL MEDICINE AND PHARMACOTOXICOLOGICAL
CLINICAL VIEWS AND PERSPECTIVES ON GLOBAL ESSENTIALS,
REGIONALLY PROTECTED, BRAND-NAME OR UNBRANDED
EQUIVALENTS, OFF-LABEL AND “ME-TOO”, NEGLECTED,
REPURPOSED, COMPLEMENTARY, PRESCRIBED AND/OR DISTRIBUTED
OVER-THE-COUNTER, DIFFERENTLY MARKETED AVAILABLE OR NOT
COUNTERFEIT DIAGNOSTIC, PREVENTIVE AND THERAPEUTIC
MEDICINAL PRODUCTS**

Carlo De Martinis⁺ and Luigi Rossini⁺⁺ ^

General Internal Medicine⁺, UPM and University of ROME 1st, La Sapienza, and Experimental
Medical Pharmacotoxicology and Clinical Service⁺⁺, UPM and Regione Marche, Italy (°)

Summary

The current variegated multitude of denominations, classes and registries of natural, synthetic and biological drugs can be managed globally at relatively low cost through the international database of adverse events and reactions (ADR), where these events are reported with full transparency, collected systematically, and checked on the actual clinical records (private, professional, public and/or published); however the same data can equally be obtained in conditions standardized according to methodologies and provisions repeatedly optimized by the WHO. These data are freely and readily available online to citizens, researchers and teachers, regulators, entrepreneurs, manufacturers, both before and after drug marketing, and also in transitional phases of biological and experimental pre-clinical research.

The current situation, laughably repetitive and clearly no longer sustainable, has been made substantially obsolete, unproductive and at the same time illiberal, oppressive and counterproductive, and shall have to be updated based on the criteria traditionally supported and adopted by the WHO-ITA / ITA-OMS, approved by the WHO. Italy is one of the six founding members of the international network that has begun here and now involves more that 79 members.

Key words: Internal Medicine, Experimental and Clinical Pharmacotoxicology, Drug Lists and Availabilities, 2009 and 2010

(°) Completed April 1, 2010. Parts of this contribution have been presented at “The Wednesday Meeting” March 31, 2010 “Generics become protagonists on the health theatre”, Civitanova Marche, Italy. ⁺, ⁺⁺ Retired on October 31, 2008. (^) Corresponding author. References listed as groups in inverse temporal order. Books, full papers and “journal papers” as complete copies, summarized and annotated available at home Archives. Tel CDM +39 071 665 378, e mail: carlodemartinis@gmail.com; Tel LR +39 071 31920, e mail rossiniluigi@hotmail.it

“ ... whoever has a great deal of internal warmth of his own will prefer to keep away from society in order to avoid giving or receiving trouble and annoyance”. Arthur Schopenhauer, *The art of controversy*.

“Difficile est satiram non scribere”. Decimus Iunius Juvenalis, *Satirae*.

The inventor of genome sequencing technology, a pioneer of systems biology and medicine [1] considers his future, called P4, preventive, personalized, preventive and participatory, and we can surely consider the commonly generalized P5 factor too, i.e. their always optimizable probabilistic trend, at least for those uses and inevitable abuses of medicinal products presented as for emoticons by current politics (i.e.: [2]). The previous interventions, predominantly of a general type [3] have addressed some aspects that reflect the competitiveness of the current state of social freedom that also distinguishes our healthcare, which nonetheless is rapidly evolving, also from the regulatory point of view, even though some issues remain sometimes confused and therefore ineffective if not actually counterproductive. There is no doubt on the desirability if not the need to be alert, especially to events happening elsewhere (Cf. [4]), where the debate is often harsh [5] and new proposals are never unanimously shared, although the general principles involved are firmly acquired [6], as we may subsequently stress here. Solutions, including brilliant ones, are not lacking, but they need to be found practicable by testing them with repeatedly standardizable criteria if they are to be considered as exemplary [7]. Other solutions that have long been awaiting our clarification and implementation with regard to the very basic classification of the properties, that can be defined as exquisitely clinical-pharmacological, will also be critically addressed and/or examined in short sections below.

1. The utilization of essential drugs

The mythical WHO Technical Report Series (TRS) 615, Geneva 1977, and the enclosed 1st Model Lists of essential drugs (which have reached the 16th edition for *adults* and the 2nd for *children* as of March 2009 (English ed., see www.who.int/medicines/publications/essentialmedicines/en/index.htm, accessed April 1, 2010) include a double list, a *core* list – reporting minimum medicine needs for a basic healthcare system, listing the most efficacious, safe and cost-effective medicines for priority conditions according to the statement of Alma Ata (1978) – and a *complementary* list, presenting essential medicines for priority diseases for which specialized diagnostic or monitoring facilities and examinations are needed. The lists are subjected to biannual updates/modifications also based on the priorities of the different disease forms in the various countries. They report, among other things, the definition of *therapeutic equivalence*, which has become the reference for generic drugs and may be also for biosimilars, referring the reader to non-proprietary names for the identification of the active principles. Although these criteria have become established with some perplexities and reservations, they have however consistently been adopted all over the world in the best academic teaching and publications. For comments on and clarifications to the WHO proposals by Italian experts see articles cited in references [8], whereas the presentations have been made by the voluntary collaborators, also WHO-ITA / ITA-OMS, from the authors' two Institutes of Ancona University, now Polytechnic University of Marche (Cf. [9]).

It is substantially advocated that *essential drugs*, including life-saving ones, be always available and provided in the least expensive formulation among those licensed, and their cost sustained by the State in the most advanced and civilized societies.

2. Some global, regional and national regulations, protections, behaviours, and costs

While the reader is referred to the international, global and regional healthcare and pharmaceutical legislation and problems (Cf. [10, 11]), it must briefly be stressed that over the last few years there has been a tendency, especially in Italy, to protect the patents of innovator / originator products, which have become the reference for the brand-name (or unbranded) equivalents (as reflected in the Italian law no. 405/01). According to the WHO definition, a *therapeutic equivalent* is a drug that can be commercialized only after the expiry of the patent and the certificate of complementary protection (CCP) of the innovator drug. The CCP, introduced in Italy with law no. 349/91, prolongs the duration of the period of exclusive exploitation of the product by the originator company by up to 18 additional years, in addition to the 20 years patent protection period, with a marketing authorization (MA). This act was superseded by EEC regulation no. 1768/92, which introduced the supplementary protection certificate (SPC), reducing the added protection to 5 years, but guaranteeing the validity of the national certificates granted before 1993. Italy has therefore approved law no. 112/02 to modify the duration of the CCP for the issue of the MA by the Italian Drug Agency (AIFA), which involves the control of requirements (Cf. [12]) according to a reduction procedure lasting 6 months per solar year, which began in 1.1.2004. After the owner's demonstration of the chemical and pharmaceutical equivalence of the generic according to the regulations of the European Medicines Agency (EMA) (Cf. [13]) and of its *bioavailability*, i.e. the rate and amount of the active principle released into the circulation, again in line with EMA provisions [13], the product is declared as population *bioequivalent* to the patented one, a conventional statistical "surrogate" of therapeutic equivalence, which is required for MA emission. At least 8 years must have elapsed since the initial authorization to the originator and at least 10 from the equivalent reference product. Mutual recognition procedures are applied for most equivalent medicines. At both the national and the local levels the same documents are required as for an MA application, which envisages product quality monitoring even after the commercialization through the announced European *post-marketing network* [12] of official laboratories and with the Italian Istituto Superiore di Sanita' (ISS), to which we will go back later to highlight the outstanding contributions, certainly not merely repetitive, of that WHO-ITA / ITA-OMS, and other European bodies, in which Italy has participated, also as one of the six founding member (membership is now over 79), and to which it has contributed by starting the global electronic network, as acknowledged by the Geneva Headquarters (Cf. [14]).

According to law decree no. 97 of 28 April 2009, coordinated with laws no. 77 of 24 July 2009 and no. 147, of 27 June 2009, which turned the decree into law, "the sale price of equivalents is ... (further) reduced by 12% ..., up to 31 December 2009, ..., the NHS, in paying pharmacies what they are owed for selling the drugs, retains ... 1.4 % of the total (which is also made up of any quotas paid for by the citizens and of conventional and legal deductions. ... For equivalents ... the quotas of the sale price before VAT... paid out to the other parties are revised as follows: drug manufacturers: 58.65 %; wholesale retailers: 6.65 %; and chemists 26.7 %. The remaining 8 % is redistributed between chemists and wholesale retailers ... ". The quota earmarked for pharmaceutical expenses, out of the total 19.3 billion € allocated to the NHS, was 13.6 % in 2009 and 18.4 % in 2010. The proposed cuts envisage further reductions in the price of generics by 1.5 billion € (off-patent and others, whose price should be cut by 60-70%, considering that hospitals already enjoy a 70 % discount) and a reorganization of distribution, with overall savings of ca. 2 billions, by entrusting AIFA with centralized procurement at the lower prices stated by

manufacturers [16]. Streamlining of off-label drugs, which has been going on for some time elsewhere, may involve contrasts (see (1)). The ruling (no. 13981/09 of 30 December 2009) of the Administrative Tribunal of Latium requiring physicians prescribing “medical specialties to state the reasons for the intolerance and ineffectiveness of an equivalent” in prescriptions, is a case in point (see examples of current and earlier costs in Table 1).

Therefore in Italy, too, not only the chemist but also the physician, who is responsible for diagnosis and prescription, is placed at the frontline, like the student and the academic researcher, by healthcare and pharmaceutical politics, with continuous analyses (rejected in the Comment, Cf. [17]), statements and critical debates, which unfortunately are never conclusive, by the various parties, even those involved indirectly, similar to those produced by the international bodies [18].

If this presentation is not sufficiently analytical, examination of the references will afford a more exhaustive picture, uncertain as it looks today. Here we highlight the outstanding successes, well beyond serendipity, of pharmaceuticals companies, which have always benefited from the undeniable contribution of academia, each with their respective activities and roles. However, university researchers are concerned and perplexed by the symptoms, which albeit not new have now become very marked, represented by the multiple failures of Big Pharma projects, which can no longer be tolerated, where more abundant funds have been invested not only to produce competitive “me-too drugs”, but especially to develop innovative routes to replace older drugs, after the failure and closure of rich and prize-winning Laboratories. The torcetrapib trial, which involved Japanese families carrying a CETP mutation, is a case in point. The drug-induced elevation of HDL lipoprotein levels killed more participants than it was intended to save, leading to early cancelling of the trial, for which 15,000 people had been recruited and 800 million US dollars had been spent. The company, given the failure to develop a new blockbuster to replace the highly successful atorvastatin – whose patent also in Italy will expire on 8 November 2011 – has not turned to other preventive or therapeutic cardiovascular drugs, considered an excessive and intolerable risk, nor has it promptly entered the field of brand-name equivalents (according to the 25 year old Waxman-Hatch Act), or of multiple medications, like a “polypill” (Cf. [19]), but rather it has decided to close down the cardiovascular drugs advanced research section, a decision that has been judged as an exemplary lack of faith in a highly successful and long-standing methodological strategy, that of the clinical trials [20]. This requires a re-examination of the generalized and topical context of our alternative project [3], which will also be addressed below.

3. Counterfeited, equivalent and biosimilar, orphan and medicinal products for neglected diseases

After stressing that it is not academia alone, but primarily the genius, investments and ability of private manufacturers, that created the new and most interesting reference drugs, it is impossible not to fear the diffusion of closures, firstly and as eventual next beginning of 2009’ 312 medicines in US developments for the still same top deadly heart and stroke diseases, particularly with the growing acceptance of comparative effectiveness research [21] extended to drug generic versions, and the needed more stringent and far outstandingly applied safety standards, being “In these uncertain times, the decision a reminder that pharmaceutical innovation is vulnerable to market forces, changes in medical practice, and regulatory requirements” [20]. The open academy, which is not, directly or indirectly, dangerously connected to market or external political forces, certainly fully agree. Nevertheless, the anti-counterfeiting task forces of the IMPACT groups sometimes still appear to have limited effectiveness, both on guaranteeing the quality of raw chemicals (just think of the heparin disaster), and on marketing and/or selling illegal clones through online shops (Cf. [22]), as well as on the application of possibly the best available methodologies to Good Laboratory Practice, animal and human experimentation, completeness of recording, transparent adherent

evaluation and public communication of what is being done. Indeed, it is astonishing that Big Pharma should now apply their resources to brand-name (and unbranded) “generic” equivalent marketing, rather than to pure innovation products, or at least to research, development and strong marketing of biosimilars. But the same equivalent products may be equal in most, but not all cases, like for instance the therapeutic effects [23]. The surrogate biokinetics markers of choice, as indeed also recommended in the most recent EMEA guidelines, raise doubts and confusion when they state for instance ([13], p 10/27) that “non-compartmental methods should be used for determination of pharmacokinetics parameters in bioequivalence studies. The use of compartmental methods for estimation of parameters is not acceptable” (see note ⁽²⁾; [24]), when the blood concentration of a product is not a biomarker indicator of effect (see note ⁽³⁾; [25]), and for the products with a narrow therapeutic range the very large acceptance confidence or fiducial inference interval for AUC-C_{max} geometrical means does not pre-indicate how much it may need to be tightened (see section 4.1.9, etc; p 15-16/27), even where now “consultation begins on automatic switch to generic drugs”, as in the UK [26]. And it is not surprising that bioequivalence testing is performed, as recommended, on so-called normal adult individuals, without any proof of the different potential reactions in non-healthy subjects or in physiologically frail individuals. Nevertheless we recommend again David Gilbert’s incredible work, a salutary preliminary endeavour [27].

A different question is that of biosimilars, which “are the hope and the future of research and will lead to a greater development of generics, now called equivalents” [28]. In the US the law grants only 5-years protection for “small” molecules and for their tests and equivalence investigations compared with those of the originator drugs. For biosimilars, i.e. the protein molecules, and for barely different “me-too” drugs, full Biologics Licensing Application (BLA) and a protection period of at least 12 years has been proposed to avoid law suits and often out-of-court transaction, as in the case of equivalent generics, like off-label drugs (Cf. [29]), plus an additional 12 years for minor variants (although this is unlikely to be accepted, since the more influential shareholders aim for the latter at a different BLA, with development aimed at the highest possible profit for the first 12 years and sale as therapeutic alternatives). The papers of Engelberg et al [30] and Garber [20] are rich in other ideas, which do not rule out the final victory of the policy of the current presidency, which is against prolonging the 5-years protection period for biosimilars, with investment by manufacturers aimed alternatively especially to the more innovative phases, as for the generics in general, etc. In any case, biosimilars, which are more complex, require preclinical and clinical research and pre- and post-marketing monitoring, including obviously the best possible pharmacovigilance, specifically on the trends of immunogenicity evolution, stringent quality control, and so forth. Therefore we present here the tribulations of clinical trials (Cf. [31]) and the urgent need to adopt as soon as possible our proposal (Cf. [13]), reiterated and discussed below in Section 5. A very significant element is that the verification of indications must be conducted expressly, not considered as automatically interchangeable [32]. It may be added that this class of drugs is often less topical than *orphan*, and that it tends more than any other to *personalized medicine*, and consequently does not ignore the global issue of rare and neglected diseases [33].

In Italy somatotropin was the first biosimilar, approved in 2006 with the specific EMEA guidelines, while others (another human growth hormone analogue, two erythropoiesis-stimulating agents, and filgrastim) have been authorized for distribution with reduction of shipping costs and a retail price reduction of 25 to 50 % compared with the originators. Market expectations are greater than ever before, since by 2015 at least 15 other patents will expire in Europe and 45 in the US [34].

4. Research, trial tribulations, and off-label, and redirected (or otherwise) discoveries

We want to start this section with two paradoxes. 1st - The cost of the traditional three-phase clinical trial is mounting so much that it is not always sustainable (Cf. Malakoff D. Spiraling costs threaten

gridlock, in [31]), particularly where and when regulator agencies insist on systematic comparative research, namely findings must show better trends throughout re-study of previous busters, and not any time vs repeated placebos only [21]. Therefore traditional multistep, multisite, double or triple-blind, randomized, cross-over studies, even those modelled on global epidemiology data, are no longer the best investment, but new originators, and even similarly financed research into biosimilars, no longer offer the best revenues as in the past, because patient groupings are of course less and less numerous due to the shift towards more personalized, individual diagnostic procedures extensively applied and finalized; in any case, the cost of a cure (up to 200,000 \$ annually for imiglucerase for Gaucher's disease; see: [30]) would be unsustainable by individuals, families, and even social, national and supranational care organizations, like the extraordinary insurance premium.

2nd – Consider the hypertension paradox [35], where the number of people with uncontrolled high blood pressure has continued to rise despite one of the most resounding medical successes of the past half-century, mostly due to failure to adopt a healthy lifestyle. This paradigmatic example also shows that clinical trials are outdated and that they may be useful only in some fields. The role of digoxin in managing acute heart failure syndromes [36], where the still inconclusive trials require a rethink, is another facet of the problem.

In [37-40] we list the contributions, from January 2009, on the issues discussed most frequently in the major general and specialist clinical journals with regard to the regulation of clinical-pharmacological trials [37], focusing on dyslipoproteinemic [38] and pharmacogenetic associations [39]. These papers, as mentioned and discussed in [14] and [31], also raise objections on the transparency and independence of regulatory organs and the ethics of not wholly legitimate interests involved in the personalized studies financed by them [40], which are especially - or better exclusively, entrusted with the transparent performance of controls on the investigations of others; on other conflicts of interest of the various potentially independent organs representing professional categories, on the need for patients and physicians to contribute disinterestedly, consistently and in a civilized way, to data collection without a predetermined selection, in order to help the updating of never definitive conclusions of the same meta-analyses; on the non-acceptance of repeatedly, globally standardized statistical-epidemiological criteria from the basic, general pre-clinical phase to the routine clinical work; etc: every reader will recognize his own preferred topics. Beware of the suicide of "seeding trials", like the 1999 ADVANTAGE trial, defined as intellectually redundant and wasteful, apparently aimed at promoting new treatments "which have little to do with science, and much to do with marketing", a masquerade of research! Nevertheless, "researchers refine in vitro test that will reduce the risk of "first in human" drug trials [41], "phase zero trials: a platform for drug development?" [42] are proposed; the "collection of data on patients' race and ethnic group by physician practices" [43] is undertaken; "an independent external validation and evaluation of a specific risk prediction [44] is advocated; and finally (!) some want to go "beyond the impact factor" [45]; in addition an articulated, complex, fatiguing "flexible blueprint for the future of drug development" [46] has been drawn up without however really coming to grips with the already obsolete issue of the quantification of placebo effects, of complementary medicine, of the inevitable social epidemiology of drug addiction and of the absolutely significant presence of off-label effects, on which premonitory reviews have been presented also by ourselves (Cf. [14, 47, 48]). It is one of the latter secondary *neglected* effects, unfortunately not at all uncommon (found in up to one third of paediatric prescription products [49]), that has given rise to one of the most bitter, bewildering and unforgettable stories of marketing through misinformation and manipulation [50]. Consciously or otherwise, the need for reforming their advertising [51] is also associated not only with the need for drug reclassification – which has repeatedly and consistently been advocated by the authors (Cf. [3], [14] (p 82, and [25]), and [47]) – but also of enhancing the sustainable treatment of this group of *orphan* diseases and drugs, starting with diagnosis [33, 52], with the *recovery*, it, too, still not

systematically structured, of reviews [53], issues that have already been addressed but need to be further discussed.

5. The WHO-ITA / ITA-WHO Pharmacovigilance Monitoring Programme involving the Marche Region and Ancona University and the continuative realization of our original epidemiological-exploratory, analytical clinical pharmacotoxicology laboratory network

Here we will not mention our abundant literature, which is summarized in the previous references. The pharmacovigilance literature of 2009 is scanty (Cf. [54]), as if the gradually obsolescing topic had become tiring and boring; nonetheless, the relevant problems as presented and discussed this far are still fundamentally unresolved and have unfortunately extended and become worse.

After being delegated by the Italian Health Minister [56] and by the 5th Meeting of the Representatives of the National Participating Centres [57], we have worked on, continuously and devotedly (Cf. note (4)), even though we have never been acknowledged by the successive national, regional and local Agencies, by the local community [58], but especially by the Medical School and the merged Hospitals, which have forgotten to complete the provisions of the official headquarters we identified (Cf. “Villa Gusso”, [59]), as well as to provide an alternative one, thus systematically opposing all development. The rich national and local (regional) funds - totalling together 551,475 € for the sole year 2008, and 535,000 € from the AIFA research budget, was a huge sum [60], will obviously require verification to establish whether they have been cautiously invested - have been integrated by our total commitment and at our personal expense while working for the University. Our original project, convergent with the views of the late Sir Richard Dole and expressed at the interregional level of our national scientific society, also through the public press [61], has been confirmed and applied in subsequent contributions, disseminated in national professional journals and also in the online journal of which we are cofounders [62]. In contrast, all the problems outlined in the previous sections, which have otherwise remained outstanding, with consequent deficiencies and inefficiencies, have the potential, today more than ever, to be developed at low or no cost if private and public, general and specialist facilities, surgeries, emergency departments, toxicology centres, and outpatient clinics, as well as more complex autonomous hospitalization, cure and rehabilitation facilities, could be persuaded to report patient histories to a single, systematically collaborative, stable interactive network, without never locally isolated superimpositions, namely that of the WHO international project. In France this structure has absorbed, for instance, the networks of toxicology centres and first aid facilities, and in Italy it has promoted the interuniversity network, for epidemiological-exploratory, analytical as well as didactic assistance, for both research and development [63]. The healthcare personnel currently not participating, e.g. those not included in any Registry (Cf. [64]), like the same studies defined as independent and then financed by AIFA projects, and even without making recourse to monitored release methods, agreed at the time [65], but respecting first of all the conditions of “overall patient load”, certainly not surreptitious, fictitious and to a certain extent privileged, theoretically predisposed ideal but limited, with reference and patient populations that must not be conditioned by rigid or flexible, nor preordained, structured criteria of recruitment, inclusion and exclusion, extended to the same cited institutive research claimed by AIFA, are not excluded. Therefore only through previous randomization, without following the approach of waiting and limiting the manufacturers’ explicit request to conduct their own studies before, during and after marketing. Without the monitoring process to be able to be used especially and/or exclusively as a “process useful to limit access to the drug”, respecting the natural variability in prescription decisions in the various areas and if necessary devising and pursuing automatic collateral studies, especially ex-post to establish any use and potential abuse of the available medicinal products, otherwise subject to the heterogeneity of goals. The exploratory, epidemiological, observational and analytical network

which now encompasses nearly 80 Countries, had initially been proposed only in similar programmes of the Office of Technology Assessment (OTA) of the US Congress (see also, Teselic RA, OTA, 12. 16. 1975, modified by Table IV, p 7, in [66]).

TABLE 1. Pharmacy prices for an over-the-counter and an ethical drug, brand-name and generic. Drugs that a) can be replaced with a less expensive product, and b) where the difference is to be charged to the patient if the GP prescribed a generic whereas the patients wants the brand-name drug.

Over-the-counter drug (paracetamol 500 mg; max 3000 mg/24 h). See: Heard KJ. Acetylcysteine for acetaminophen poisoning. N Eng J Med 2008;359:285-289, and Acetaminophen poisoning, Letters to the Editor, Id 2008;359:1962-1965.

Producer	Drug			
	Brand name	Generic	20 tabs	30 tabs
Angelini	Tachipirina		4.24 €	5.00 €
Bayer	Sampirina		2.59	
Abogen	Acetamol		2.80	
Teva		Paracetamol	3.33	5.00

Ethical prescription drug (Simvastatin tabs 10, 20 and 40 mg). (°) Source: Informatore Farmaceutico OEMF Int 1998.

Producer	Drug					
	Brand name	Generic	10 mg	20 mg	20 mg	40 mg
			20 tabs	10 tabs	28 tabs	28 tabs
MSD	Sinvacor		4.27€ (°) 51.700 L.re	4.94€ 27.600 L.re	10.54€	15.80€
Sigma Tau	Sivastin		4.70 (°) 55.300 L.re	5.50 27.600 L.re	10.74	16.20
Progefarma	Lipimil				9.24	14.70
Teva		Simvastatina	3.19	4.14	9.24	9.24

Note ⁽¹⁾. *Non-approved clinical indications*

“Transcription on the regional pad of drugs prescribed by a specialist for clinical indications not included in the summary of product characteristics of the Health Ministry entails a personal responsibility of the GP. However such prescription is legal if the written consent of the patient is previously obtained. In such case the patient is charged the full price of the product in presence of authoritative medical literature confirming the rationale of the prescription (as per law no. 94 / 1998). In the absence of authoritative literature to warrant it, the prescription of drugs for clinical indications that have not yet been recognized is to be considered as a trial and is subject to the provisions of the decree of the Health Minister of 27 April 1992 and subsequent modifications, whereby the cost of trial drugs is to be sustained by the sponsoring drug manufacturer and not unduly charged to the NHS (encl 1, par. II, 2.3, d), it is under direct responsibility of the experimenter (encl 1, par. II, 2.5, j), and requires written informed consent by the patient and previous authorization by an ethics committee. Prescriptions for unapproved clinical indications charged to the NHS could be considered as fraud against the state (art. 640 penal code); in case of adverse side-effects the patient could sue for damages for culpable liability (verdict no. 3599 of 18 April 1997 of the Third Section of the Supreme Penal Court). The GP can refer the case to the

Medical Association, the local NHS Director and the Director of the hospital from which the putatively improper transcription request proceeds". *Mauro Marin, general practitioner and expert in legal healthcare issues. Pordenone, mail 31. 3. 10. 10:00.*

Note ⁽²⁾ *Salient facts of compartmental and non-compartmental model pharmacotoxicokinetics, from [24].*

While comparative dynamics tests of any drug require a minimum of three dosages to estimate the needed basic dose-effect linear slope and calculate their geometric mean (m_g and / or x_g) being one value spent as a degree of freedom, to infer a linear AUC kinetics, the same three doses must be applied. Thereafter, through convolution, is it possible to evaluate at least the simplest fitting to a first order simultaneous linear model, by Fick's law, both for the pre-eminent absorption, and the superimposed next dominant elimination kinetics trends. For absorption: $dx/dt = k_1t$; $x = a(1 - e^{-k_1t})$; $\ln(a - x) = \ln a - k_1t$; $\log(a - x) = (\log a - k_1t) / 2.303$; for elimination: $dx/dt = -k_2t$; $x = x_0e^{-k_2t}$; $\log x = (\log x_0 - k_2t) / 2.303$. The distribution equation, which underlies the integral AUC, by convoluting the function $x_0k_1e^{-k_1t}$ for e^{-k_2t} , for the model: $X_1 \longrightarrow X_2 \longrightarrow X_3$, is:

$$X_2 = x_0 [k_1/(k_2-k_1)](e^{-k_1t} - e^{-k_2t}),$$

$$t_{\max} = [(1/(k_2-k_1)) \ln(k_2/k_1)], \text{ and}$$

$$C_{\max} = X_0 (k_2/k_1)[k_2/(k_2-k_1)],$$

where C_{\max} is linear with the dose administered, t_{\max} does not change with the various doses, and $2 t_{\max}$ is the flexion point, since it is also possible to estimate k_1 and k_2 with graphic semilog derivation (e.g. again with the least squares method), whereas Cl (clearance, in l/h) = dose (mg) / AUC (mg x h)/l; $V = \text{dose} / C_0$; $t_{1/2} = 0.693 V / Cl$; $k = 0.693 / t_{1/2} = C / V$, and bioavailability, F with reference to $AUC_{\text{test}} / AUC_{\text{reference}}$ with regard to the interval of fiducial limits, where P measures the confidence or fiducial inference according to Student's t distribution = $(x_g - \mu) / s_m$, where s_m the standard error or standardized deviation of the mean, and at $t = +/- 10\%$ is:

$$P (-t_{0.10} \leq (x_g - \mu) / s_m \leq t_{0.10}),$$

equal to 0.8 – 1.25 (asymmetric compared with 1 for log transformation). The complete set of kinetics parameters is of 7 elements, where: $Cl \times \text{turnover time} = V$; $\text{turnover time} \times \text{turnover number} = \text{permanence time}$; $\text{permanence time} \times \text{yield} = \text{occupancy}$, and by selecting 4 of them, the others, up to 7, can be obtained. For non-linear enzyme (and receptor) systems, where kinetics trends are not (multi)exponential but hyperbolic, % of reaction velocity, $v = (V_{\max} \cdot s) / (K_m + s)$, intrinsic $Cl V / C = V_{\max} / (K_m + C)$, or at very low concentration, circa = V_{\max} / K_m .

Note ⁽³⁾ *From [25], Chapter 9 (summarized and modified) – Pharmacodynamics. Dose-effect relationship. Cases where the concentration of a drug is not a good indicator of effect.*

I – Drugs used at concentrations that produce maximal effect: in this “window” different, also adverse, events can be recruited, which exhibit higher DE_{50} ;

II – Fast acting drugs, irreversible (e.g. aspirin, early MAO inhibitors);

III – Delayed distribution, when the main site of action is found in a compartment where the drug has a slow distribution (e.g. digoxin; the effect increases when its concentration falls due to redistribution: anti-clockwise hysteresis of the dose-effect relationship);

IV – Acute tolerance (tachyphylaxis; clockwise hysteresis of the dose-effect relationship): e.g. cocaine and indirect sympathomimetic amines like pseudoephedrine and amphetamine;

V – Hormesis (inverse effects at the lower concentrations);

VI – “Wrong” effect measurement, e.g. warfarin, where prothrombin time increases as its concentration decreases. The rate of onset of the effect is a function of the rate of decay of the existing clotting factors, whereas the direct effect that is exerted on their rate of synthesis corresponds to the drug’s concentration;

VII – Active metabolites not measured by the analytical method used, e.g. first pass of several oral beta-antagonists;

VIII – Enantiomers, with optical isomers having different kinetic and dynamic properties, e.g. again various beta-adrenergic antagonists;

IX – Protein bond saturability and analytical measurement of total levels and of the effects associated to unbound fractions, e.g. non-linear phenytoin pharmacokinetics.

Note ⁽⁴⁾. *First Marche Region Healthcare Conference, Loreto 21-22 June, 2001. Abstract from the Book of Proceedings.*

Ancona, 14 June 2001, prot. F 297. **Operative Unit of Clinical Pharmacology and Toxicology. Specific, excellence, planning and ongoing activities.**

Since 1973 the Service, the only one in the whole of Marche Region, has started, developed, and consistently met the regional requirements of teaching, research and joint clinical activities, suitable for the reference sector coordinated there on behalf of the University, namely Degree courses, Specialization, short Diploma courses, etc, by the following main activities, decided every year aiming specifically at the innovative advancement of the University and of local and regional healthcare bodies: 1) *Assays and auto-classification techniques* of iso-receptors, supraenzymatic-supramolecular systems and groups of analogues, from experimental analytical pharmacotoxicology to clinical-exploratory-epidemiological and socio-economic pharmacotoxicology; 2) *Redox and phosphorylation potentials with compartmental integration*: Implementation of non-invasive electro-physio-pharmacotoxicological techniques, spectrophotofluorimetric techniques extended to the near infrared, mass spectrophotometry and multinuclear magnetic resonance. The acquisition of accessory microimaging methods to analyse easy-to-collect bioptic and biomedical samples, has already been decided and is in progress; 3) *Routine therapeutic monitoring* of chemical-clinical specialist, applied pharmacotoxicokinetic parameters of more than 80 diagnostic products (and metabolites) and of current therapeutic, maintenance, rehabilitation or leisure-time use/abuse of multiaddiction drugs (reference programmes for Marche Region), antidotes, antidoping and antipollution products as well as galenic preparations, generics, bioequivalents and biosimilars that are going to be distributed soon; 4) *Pharmacotoxicoepidemiology*: Creation and development of the pre- and post-marketing international pharmacovigilance ITA-OMS / WHO-ITA system; 5) *Time series pharmacotoxicokinetics*: power spectra of supra- and intracellular heart, tension, respiratory, and metabolic fluctuations interfaced as functional parameters with analytical, metabolic, non-invasive, chemical-clinical and clinical-specialist parameters; 6) *Multiparameter study of peptidergic-purine-pyrimidinergic, non-adrenergic, non-cholinergic, nitrinergic systems* (national and international projects involving CNR, ITA-USA and ITA-Canada; collaboration with the Canadian National Research Council and Manitoba university); 7) *Experimental and clinical pharmacotoxicological caspase modulation in apoptotic cycles*; 8) *Theranostics and analytical, chemical-clinical and exploratory-epidemiological pharmacotoxicogenomics*, initially involving

iso-guanylyl cyclase and NO-synthase modulation (current collaborative project with the integrated Biology, Physiology and Pharmacology Department, the Clinical Pharmacology Section and the Molecular Medicine Section of Houston Medical School, Houston, Texas); 9) *Human pharmacotoxicology Section* of the IMO Interuniversity Centre, Molecules and Organisms, Siena University.

Complete structuring of the methods of the analytical laboratory was started and pursued in collaboration with the Pharmaceutical Service of the local hospital by applying International quality assurance standards and in the framework of the objectivity statistical validations needed for the *Pharmacotoxicology vigilance project*, set up here as the University-Hospital national collaborative centre with the first 6 member Countries (at present 48) of the WHO system. In particular, the objectivity analysis of phase IV has been extended with respect to the original project as a *reference excellence activity* practiced there for the first national trial (naloxone), in view of the *replacement of conventional trials with comprehensive experimentation, including all patients involved in the use /abuse of the medication*, whose IT structuring has required the implementation of exploratory-epidemiological, iterative auto-classification programmes from the experimental to the clinical phase. A unique project design directed at the individual patient, avoiding the randomizations and limitations of current trials designs.

The excellence tasks and activities of the Operative Unit have included, in line with the opinion of 26 January 1979 of the Consiglio Superiore di Sanità, accepted on 28 November/2 December 1983 by the Joint Session of the EC Committees, International Chemical Agent Safety Programme and WHO European Regional Office (*Cf, "L' attivita' del Servizio e' principalmente sviluppata quale consulenza e specialistica di laboratorio"*) the clinical-hospital activities of: a) *Co-assistance to drug addicts*; b) *Drug treatment in wards carrying out trials of new products and/or formulations*; c) *Pharmacovigilance tests*; d) *Monitoring of bound and/or unbound concentrations of drugs (and metabolites) in easy-to-collect biopsy samples and tissues (e.g. blood; urine, CSF, aqueous humour)*; e) *consultation concerning drug-related risks of teratogenesis, carcinogenesis, mutagenesis and abortion*; f) *Participation in the drawing up and management of vade mecum-prontuaries for internal use*; g) *Collaboration with ICUs, emergency departments and dialysis centres*; h) *innovative and/or important, specialist diagnostic including radiodiagnostic procedures (e.g. for transmitter and modulator metabolism; early toxicity markers; phenotypic and genetic receptor markers: theranostics and pharmacogenetics)*. They have been included in document no. 36 of 28 January 1988 of the local NHS body and Municipalities Association, in the relevant article of the Marche regional law no. 7 of 3 March 1982 and in the updated Region/University collaboration agreements. The Clinical Pharmacology section of the Italian Pharmacology Society has more recently updated and subjected them to econometric evaluation also using our contributions –original prototypes and joint WHO documents- in particular to multi-interdisciplinary verification based on current guidelines and therapeutic protocols, of database implementation and vigilance and utilization registers, of essential drug lists, prescription and adherence to medications, and relevant monitoring methods, as included in the paradigmatic divisions of disciplinary categories already practiced in our Country and University. *The joint decision confirms that the participation of the Medical School to the achievement of the goals of the National and Regional Health Service takes the form of the Service of the Operative Unit, first structure charged with the task of performing drug information and documentation activities.*

(Updated extract of Paper F55 of 3 March 2000 “Il Polo Universitario- Ospedaliero di Ancona. Il Servizio di Farmacologia clinica e Tossicologia”, written upon the Dean’s invitation, distributed and in press in: Memorie e Rendiconti, Proc. Acc March Scienze, Lettere ed Arti, Ancona, Italy).

References

- [1] Hood L. A doctor's vision of the future of medicine. Newsweek July 6/July 13. 2009;46-47.
- [2] Ruta C. Medicina predittiva, Programma della Dir Serv Salute Regione Marche. Il Messaggero Ancona Salute 20. 3. 2010, p 5.
- [3] Rossini L. Drugs and the future. Pharmacologyonline 2005;1:12-44; Rossini L. Sperimentazione dei farmaci e farmacovigilanza. New Entries in Pharmacology 2006;I, 1:3-22.
- [4] Murray CJL, Frenk J. Ranking 37th – Measuring the performance of the US health care system. N Eng J Med 2010;362:98-99; Orentlicher D. Health care reform. JAMA 2009;301:1816-1818; Conway PH, Clancy C. Transformation of health care at the front line. JAMA 2009;301:763-765; Antos JR. Symptomatic relief, but no cure - The Obama health care reform. N Eng J Med 2008;359:1648-1649; Blumenthal D. Primum non nocere - The McCain plan for health insecurity. N Eng J Med 2008;359:1645-1647; Editorial. Health care reform and the presidential candidates. N Eng J Med 2008;359:1537-2092.
- [5] Chan PS, Jain R, Nallmothu BK, Berg RA, Sasson C. Rapid response teams. Arch Intern Med 2010;170:18-26; Davidoff F. Heterogeneity is not always noise. Lessons from improvement. JAMA 2009;302:2580-2586.
- [6] Ramsey PG, Miller ED. A single mission for academic medicine. Improving health. JAMA 2009;301:1475-1476; Kirch DG, Vernon DJ. The ethical foundation of American medicine. In search of social justice. JAMA 2009;301:1482-1484.
- [7] Margolis P, Halfon N. Innovation networks. A strategy to transform primary health care. JAMA 2009;302:1461-1462; Federoff HJ, Gostin LO. Evolving from reductionism to holism. Is there a future for systems medicine? JAMA 2009;302:994-996; Dreyer NA, Garner S. Registries for robust evidence. JAMA 2009;302:790-791.
- [8] Editoriale, Farmaci essenziali e *primary health care*: 30 anni dal WHO TRS 615 e da Alma Ata. BiF 2008;XV:2-4; Borolossy E. Il concetto di farmaco essenziale. Il Nuovo Boll Farmacol Clinica 1988;11:135-137; Concettoni C, Galeazzi G, Re L, Rossini L. Liste modello internazionali, prontuari nazionali, regionali e locali vs indicazioni e attivita' terapeutica. Il Nuovo Boll Farmacol Clinica 1988;11:129-134; Donatelli L. O.M.S. e selezione dei farmaci. Il Nuovo Boll Farmacol Clinica 1986;9:187; Concettoni C, Rossini L. L' uso dei farmaci essenziali. Il Nuovo Boll Farmacol Clinica 1986;9:188-190.
- [9] Updated WHO List of Essential Drugs, edited by WHO-ITA/ITA-OMS (Denomination approved by the World Health Congress): 5th revision, WHO Drug Inf 2:31-41. Il Nuovo Boll Farmacol Clinica 1988;11:138-156; 4th revision, TNS n 722. Il Nuovo Boll Farmacol Clinica 1986;9:191-233; TNS n 685. Il Nuovo Boll Farmacol Clinica 1982;5:107-144; 2nd revision, TNS n 641. Il Boll Farmacol Clinica 1982;2:Suppl 1-40.
- [10] Knowles SM. Fixing the legal frame work for pharmaceutical research. Science 2010;26:1083-1084; Dukes G. The law and ethics of the Pharmaceutical Industry. Elsevier, San Diego, CA, USA 2006; Santoro MA, Gorrie TM, Edts. Ethics and the pharmaceutical industry. Cambridge Un Press 2005; O'Neill O. Autonomy and trust in bioethics. Cambridge Un Press 2002.

[11] Letters to the Editor: FDA drug information that never reaches clinicians. *N Eng J Med* 2010;362:561-563; Hubbard WH. Health care reform. Can the food and drug administration ensure that our pharmaceuticals are safely manufactured? *Arch Intern Med* 2009;169:1655-1656; Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. *JAMA* 2009;302:2679-2685; Woodcock J. A difficult balance – pain management, drug safety, and the FDA. *N Eng J Med* 2009;361:2105-2107; Schwartz LM, Woloshin S. Lost in transmission – FDA drug information that never reaches clinicians. *N Eng J Med* 2009;361:1717-1720; Bertolini R, Italy. Five candidates compete for regional director of WHO-EURO. *The Lancet* 2009;374:865; Moreno SG, Sutton AJ, Turner EH, Abrams KR, Cooper N, et al. Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal. *Brit Med J* 2009;339:494-498; DA, Sasich LD, Sukkari SR. Improving access to FDA reviews and documents. *JAMA* 2009;302:2204-2205; Epstein RM, Peters E. Beyond information. Exploring patients' preferences. *JAMA* 2009;302:195-197; O'Connor AB. The need for improved access to FDA reviews. *JAMA* 2009;302:191-193; Miller JD. FDA performance goals for approving drugs and biologics. *JAMA* 2009;302:189-191; Duncan JR, Evens RG. Using information to optimize medical outcomes. *JAMA* 2009;301:2383-2385; Gostin LO. Regulating the safety of pharmaceuticals. The FDA, preemption, and the public's health. *JAMA* 2009;301:2036-2037; Fisher ES, Berwick DM, Davis K. Achieving health care reform – How physicians can help. *N Eng J Med* 2009;360:2495-2497; Hamburg MA, Sharfstein JM. The FDA as a public health agency. *N Eng J Med* 2009;360:2493-2495; Okie S. A to-do list for the new FDA Commissioner. *N Eng J Med* 2009;360:1373-1378; Okie S. Multinational medicines - Ensuing drug quality in an era of global manufacturing. *N Eng J Med* 2009;361:737-740; Adler JR. Ethical and scientific implications of the globalization of clinical research. *N Eng J Med* 2009;360:2792-2793; Glickman SW, McHutchinson JG, Peterson ED, Cairns CB Harrington RA, et al. Ethical and scientific implications of the globalization of clinical research. *N Eng J Med* 2009;360:816-823; Hawkes N. Nice goes global. *Brit Med J* 2009;338:266-297; Steinbrook R. Saying no isn't NICE - The travails of Britain's national Institute for health and clinical excellence. *N Eng J Med* 2008;359:1977-1980; De Vogli R, Gimeno D, Kivimaki M. Socioeconomic inequalities in health in 22 European countries. *N Eng J Med* 2008;359:1290-1291.

[12] Anonymous. BiF Online Speciale, Rapporto OsMed 2008 n 8, 21 July 2009; Editorial. La via italiana agli studi di post-marketing. *BiF* 2008;XV:145-146; Workshop AIFA 27.3.2008 Farmaci equivalenti. *BiF* 2008;XV:97-140; Anonymous. In Europa la farmacovigilanza fa rete. *BiF* 2008;XV:154-155; Medicinali equivalenti e medicinali di marca. Approfondimenti su bioequivalenza, qualita' e sostituibilita'. *Assogenerici* February 2008; Anonymous. Equivalenti: tra legittimi quesiti e leggende metropolitane. *BiF* 2007;XIV:147-153; Anonymous. Farmaci equivalenti e corretto uso dei farmaci. La prima campagna di comunicazione ai cittadini dell' AIFA. *BiF* 2007;XIV:55-56.

[13] EMEA, Committee for medicinal products for human use. Guidelines on the investigation of bioequivalence. Doc Ref CPMP/EWP/QWP/1\$01/98 Rev 1, London, 20 January 2010.

[14] Rossini L. Pre- and post-marketing pharmacovigilance: The myths of the placebo effects and of the off-label use of drugs. Presented on 19th May, 2008 at the Accademia Marchigiana Scienze, Lettere ed Arti, Ancona. *Pharmacologyonline* 2008;2:80-94; 1211 Geneva 17 M10/07/22(2), 11 January 1980: "... We also greatly appreciate your offer to receive the next meeting of representatives of national centres in Ancona. Having regard to your initiative in establishing the first computer terminal link with the WHO Collaborating Centre in Uppsala, your centre has unique claim for consideration. Dr J.F. Dunne, Senior Medical Officer Pharmaceuticals, WHO Headquarters, Geneva.

[15] Siva N. The drug price is right-or not? *The Lancet* 2009;373:1326-1327; Eichler H-G, Abadie E, Raine JM, Salmonson T. Safe drugs and the cost of good intentions. *N Eng J Med* 2009;360:1379-1380; Collier J. Changes to the regulation of drug prices in the UK. *Brit Med J* 2009;338:64; Faunce T, Lofgren H. Editorial. Drug price reforms: the new F1-F2 bifurcation. *Aust Prescr* 2007;30:138-140 (See The full Australian Prescriber Archives in: www.australianprescriber.com).

[16] Gli sprechi. Farmaci, la Regione smentita dal commissario ad acta. *Il Messaggero*, 24.3.2010, p 5; Gli sprechi. Farmaci, scatta l'indagine sulla Regione Lazio. *Il Messaggero*, 23.3.2010, p 5; E' il brand che attira le risorse migliori. *Il Sole 24 Ore* 22.3.2010, p 26; Dal commercio ai farmaci liberalizzazione frenata. *Id, id*, p 16; In corsia il deficit continua a crescere. *Id, id*, p 3; Farmaci: Fazio apre il tavolo. *24 ORE Sanita'* 9-15. 2. 2010, p 5; Farmaci: mancano 2,9 mld. *24 ORE Sanita'* 2-8. 2. 2010, p 5; Clement FM, Harris A, Li JJ, Yong K, Lee KM, Manns BJ. Using effectiveness and cost-effectiveness to make drug coverage decisions. *JAMA*, 2009;302:1437-1443; Fuchs VR. Cost shifting does not reduce the cost of health care. *JAMA* 2009;302:999-1000.

[17] Tremblay M. Commentary. Risks of doing as the Romans do. *Brit Med J* 2009;338:806-807; Garattini S, Chalmers I. Patients and the public deserve big changes in evaluation of drugs. *Brit Med J* 2009;338:804-806; Goldacre B, Lawton V. Is the conflict of interest unacceptable when drug companies conduct trials on their own drugs? Yes/no. *Brit Med J* 2009;339:1286-1287; Cf. Law no. 326.03, Art 8, par 2 AIFA is instituted as of 1 January 2001. (next art.) ... Companies are charged 5% of the overall amount of the expenditure they declared for promotion activities the previous year Fifty per cent of resources constitute the National fund for the utilization of orphan drugs for rare diseases, research for comparative activities (Art 19), etc. *BifOnline: www.bif-online.it* . Anonymous. Attivita' editoriali dell' AIFA, *BiF* 2008;XV:189-190; *BifOnline Speciale* (previously cited) 2009, 21 July, *Rapporto OsMed* 2008, L' assistenza farmaceutica nel 2008, Appendice A, p 245 segg.

[18] Lo B. Serving two masters – Conflicts of interest in academic medicine. *N Eng J Med* 2010;362:669-671; Ferrari P. Iperprescrizione a due facce. *24 ORE Sanita'* 2-8. 2. 2010, p 26; Wolf MS, Davis TC, Bass PF, Curtis LM, Lindquist LA, et al. Improving prescription drug warnings to promote patient comprehension. *Arch Intern Med* 2010;170:50-56; Lurie N. The need for science in the practice of public health. *N Eng J Med* 2009; 361:2571-2572; Morris L, Taitsman JK. The agenda for continuing medical education – Limiting industry's influence. *N Eng J Med* 2009;361:2478-2482; Fuchs VR. Eliminating “waste” in health care. *JAMA* 2009;302:2481-2482; Baron RJ. The chasm between intention and achievement in primary care. *JAMA* 2009;301:1922-1924; Freed GL, Stockman JA. Oversimplifying primary care supply and shortages. *JAMA* 2009;301:1920-1922; Capitol Health Call. Unbiased drug information. *JAMA* 2009;301:1868; Greenland P. Editorial. Time for the medical profession to act. *Arch Intern Med* 2009;169:829-831; Jonas WB. Editorial. Scientific evidence and medical practice. *Arch Intern Med* 2009;169:649-650; Roman G. The Roman article: Read it again – in the same journal. *JAMA* 2009;301:1382-1383; G Cornell. Industry attack on academics. *Brit Med J* 2009;338:626-628; Schiff GD, Galanter WL. Promoting more conservative prescribing. *JAMA* 2009;301:865-867; Letters to the Editor. Internet-based education for health professionals. *JAMA* 2009;301:598-600; Kmietowicz Z. Individual drug firms must stop paying for medical education. *Brit Med J* 2009;338:313; Collier J. Doctors, patients, and the pharmaceutical industry. *Brit Med J* 2009;338:308; Krumholz HM, Ross JS. Analysis - doctors, patients, and the drug industry: Partners, friends, or foes? *Brit Med J* 2009;338:326-329; Steinbrook R. Physician – Industry relations – Will fewer gifts make a difference? *N Eng J Med* 2009;360:557-559; Sokol DK. When can doctors stay away?. *Brit Med J* 2009;338:270; Steinbrook R. Online disclosure of physician – Industry relationships. *N Eng J Med* 2009;360:325-327; Coombes R. The pharmaceutical industry is stepping in to fill the therapeutic

void. *Brit Med J.* 2009;338:70-71; Hartzband P. Money and the changing culture of medicine. *N Eng J Med* 2009;360:101-103.

[19] The Indian Polycap Study. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomized trial. *The Lancet* 2009;373:1341-1351.

[20] Garber AM. An uncertain future for cardiovascular drug development? *N Eng J Med* 2009;360:1169-1171.

[21] Bronk RH. Possible outcomes of comparative effectiveness research. *JAMA* 2009;302:194-195; Alexander GC, Stafford RS. Does comparative effectiveness have a comparative edge? *JAMA* 2009;301:2488-2490; Garber AM, Hlatky MA. Editorial. The confirmatory trial in comparative-effectiveness research. *N Eng J Med* 2009;360:1498-1499; Naik AD, Petersen LA. The neglected purpose of comparative-effectiveness research. *N Eng J Med* 2009;360:1929-1931; Avorn J. Debate about funding comparative-effectiveness research. *N Eng J Med* 2009;360:1927-1929; Garber AM, Tunis SR. Does comparative-effectiveness research threaten personalized medicine?. *N Eng J Med* 2009;360:1925-1927.

[22] Bif Editorial, Contraffazioni, paure e qualita' dei medicinali; Contraffazione dei medicinali: un brutto affare; Eparine: il punto della situazione. *BiF* 2008;XV:49-53, 56-60.

[23] Anonymous. Farmaci generici rivisitati. *The Medical Letter on Drug and Therapeutics, Italian Ed* 2010;XXXIX(n 1323 USA Ed):1-2; Letters to the Editor: Equivalence of generic and brand-name drugs for cardiovascular disease. *JAMA* 2009;301:1654-1656; Dueñas-Laita A, Pineda F, Armentia A. Hypersensitivity to generic drugs with soybean oil. *N Eng J Med* 2009;361:1317-1318; Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease. A systematic review and meta-analysis. *JAMA* 2008;300:2514-2526 (Summarized in *BiF* 2009;XVI:38-42); Letters to the Editor: Generic Medicines. *Aust Prescr* 2007;30:88-90; Hassali A, Stewart K. Editorial. Quality use of generic medicines. *Aust Presc* 2004;27:80-81; Birkett DJ. Generics – equal or not? *Aust Prescr* 2003;26:85-87.

[24] Rossini L, Rossini P. Requirements for the assessment of pharmacokinetic, pharmacodynamic and mixed population models and some topic considerations: A seminar. *Pharmacologyonline* 2007;2:48-72; A Rescigno, G Segre La cinetica dei farmaci e dei traccianti radioattivi. *Ed Univ Boringhieri Torino* 1961; L Saunders, D Ingram, SHD Jackson. *Cinetica dei farmaci nell' uomo. Un corso di esperimenti simulati. 1st Italian presentation* edited by the Members of the Biomedical Modelling: Pharmacokinetics and Bioengineering PhD course, Stamperia Universitaria, Siena 1988.

[25] DJ Birkett. *Farmacocinetica facile, 1st Italian monthly presentation in TEMA Farmacia UTET Milano*, edited by the Members of the Istituto di Medicina sperimentale e clinica, Ancona University, 1991-1993; DJ Birkett and Australian Prescriber. *Pharmacokinetics made easy, The second edition. McGraw-Hill, 2010.*

[26] Mayor S. Consultation begins on automatic switch to generic drugs. *Brit Med J* 2010;340:c135.

[27] Gilbert D. *The Normals (2004). I Normali - Professione cavia. Romanzo Bompiani. RCS Libri SpA Milano 2007.*

[28] Pieri E. Comunicazione personale. Tavola rotonda I generici diventano protagonisti sulla scena della salute. 31 March 2010, Civitanova, Italy.

[29] Tanne JH. Merck discloses \$3.7m paid to US doctors for speeches over 92 days. *Brit Med J.* 2009;339:989; Tanne JH. Pfizer agrees to pay record fine of \$2.3 billion for promotion of off-label use of four drugs- *Brit Med J* 2009;339:591; Tanne JH. US sues company for off-label promotion of drugs for children. *Brit Med J.* 2009;338:733; Kmietowicz Z. Eli Lilly pays record fines of \$1.4bn for promoting off-label use of olanzapine for common disorders. *Brit Med J.* 2009;338:191.

[30] Engelberg AB, Kesselheim AS, Avorn J. Balancing innovation, access, and profits – Market exclusivity for biologics. *N Eng J Med* 2009;361:1917-1919.

[31] Science SpecialSection Clinical Trials. *Science* 2008;322:209-223.

[32] RA McKinnon. Biosimilars are not (bio)generics. Editorial. *Aust Prescr* 2009;32:146-147.

[33] Anonymous. Drug development for neglected diseases: pharma's influence. *The Lancet* 2010;375:2; Kuehn BM. NIH Program to boost pipeline for drugs to treat rare and neglected diseases. *JAMA* 2009;302:133-134; Voelker R. Attention sought for neglected diseases. *JAMA* 2009;301:1755-1756; Anonymous. Pharmaceuticals, patents, publicity...and philanthropy?. *The Lancet* 2009;373:693; Leonard JV, Richmond S. Pricing of orphan drugs. *The Lancet* 2009;373:462; Kesselheim AS. Drug development for neglected diseases – The trouble with FDA review vouchers. *N Eng J Med* 2008;359:1981-1983.

[34] Fioravanti F. Lo sbarco in clinica dei biosimilari. *Corriere Medico* 18. 2. 2010, p 11.

[35] Letters to the Editor. The hypertension paradox. *N Eng J Med* 2009;361:2195-2197; Chobanian AV. The hypertension paradox – More uncontrolled disease despite improved therapy. *N Eng J Med* 2009;361:878-887; Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Eng J Med* 2009;361:2153-2164; Greenfield JR, Miller JW, Keogh JM, Henning E, Satterwhite JH, et al. Modulation of blood pressure by central melanocortinergic pathways. *N Eng J Med* 2009;360:44-52.

[36] Gheorghide M, Braunwald E. Reconsidering the role of digoxin in the management of acute heart failure syndromes. *JAMA* 2009;302:2146-2147; Bauer A, Gawaz M. Sensitive cardiac troponin assays. *N Eng J Med* 2009;362:2575; Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): A multicentre, randomized, placebo-controlled, parallel-group-dose-finding phase IIb. *The Lancet* 2009;373:1429-1439; Jankowska EA, Rozentryt P, Ponikowska B, Hartman O, Kustrzycka-Kratochwil D, et al. Circulating estradiol and mortality in men with systolic chronic heart failure. *JAMA* 2009;301:1892-1901; Piña IL, O'Connor C. BNP-Guided therapy for heart failure. Editorial. *JAMA* 2009;301:432-434; Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, et al. BNP-Guided vs symptom-guided heart failure therapy. *JAMA* 2009;301:383-392.

[37] Basch E. The missing voice of patients in drug-safety reporting. *N Eng J Med* 2010;362: 857-869; Eldridge S, Kerry S, Torgerson DJ. Research methods & reporting. *Brit Med J* 2010;340:36-39; Lo B, Grady D. Strengthening institutional review board review of highly innovative interventions in clinical trials. *JAMA* 2009;302:2697-2698; Fisher JA. Medical research for hire: The political economy of pharmaceutical clinical trials. *JAMA* 2009;302:2603; Hennekens CH, DeMets D. The need for large-scale randomized evidence without undue emphasis on small trials, meta-analyses, or subgroup analyses. *JAMA* 2009;302:2361-2362; Letters to the Editor. Participating in biomedical

research. *JAMA* 2009;302:2200-2202; Shaw K, Cassel CK, Black C, Levinson W. Shared medical regulation in a time of increasing calls for accountability and transparency. *JAMA* 2009;302:2008-2014; Carsten Tfelt-Hansen P. Unpublished clinical trials with sumatripan. *The Lancet* 2009;374:1501-1502; Kuehn BM. FDA steps up efforts to find, remove violators of clinical trial regulations. *JAMA* 2009;302:1739-1741; Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. *Arch Intern Med* 2009;169:1756-1761; D'Agostino RB. The delayed-start study design. *N Eng J Med* 2009;361:1304-1306; Letters to the Editor: Tort claims and federal regulation of medical devices vs pharmaceuticals. *JAMA* 2009;302:1169-1170; Mathieub S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA* 2009;302:977-984; Weinfurt KP, Hall MA, King NMP, Friedman JY, Schulman KA, et al. Disclosure of financial relationship to participants in clinical research. *N Eng J Med* 2009;361:916-921; Rodwin MA. The case for public ownership of patient data. *JAMA* 2009;302:86-88; Kilo CM, Larson EB. Exploring the harmful effects of health care. *JAMA* 2009;302:89-91; Schaefer GO, Emanuel EJ, Ertheimer A. The obligation to participate in biomedical research. *JAMA* 2009;302:67-72; Schnitzbauer A, Lamby PE, Mutzbauer I, Zuelke C, Schlitt HJ, et al. Europe gets null points for harmony in trials. *Brit Med J* 2009;338:1302-1304; Wood AJJ. Progress and deficiencies in the regulation of clinical trials. *N Eng J Med* 2009;360:824-830; Rennie D, Chalmers IC. Assessing authority. *JAMA* 2009;301:1819-1821; Psaty BM. Conflict of interest, disclosure, and trial reports. *JAMA* 2009;301:1477-1479; Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JPA. Reporting and interpretation of SF-36 outcomes in randomized trials: Systematic review. *Brit Med J* 2009;338:152-155; Preference Collaborative Review Group. Patients' preferences within randomized trials: Systematic review and patient level meta-analysis. *Brit Med J* 2009;338:85-88; Fleming TR. Identifying and addressing safety signals in clinical trials. *N Eng J Med* 2008;359:1400-1402; Kent DM, Thaler DR. Stroke prevention – Insight from incoherence. *N Eng J Med* 2009;359:1287-1289; Anonymous. I dati degli studi clinici registrati nell' OsSC e l'apertura al pubblico. *BiF* 2006;XIII:4-8; Editorial. OsSC, ingresso libero. *BiF* 2006;1-3.XIII.

[38] Mitka M. Cholesterol drug lowers LDL-C levels but again fails to show clinical benefit. *JAMA* 2010;303:211-212; Kastelein JJP, Bots ML. Statin therapy with ezetimide or niacin in high-risk patients. *N Eng J Med* 2009;361:2180-2183; Blumenhal RS, Michos ED. The HALTS trial - Halting atherosclerosis or halted too early? *N Eng J Med* 2009;361:2178-2180; Gaziano JM, Gaziano TA. Simplifying the approach to the management of dyslipidemia. *JAMA* 2009;302:2148-2149; Hingorani AD, Psaty BM. Primary prevention of cardiovascular disease. Time to get more or less personal? *JAMA* 2009;302:2144-2145; Califf RM, Harrington RA, Blazing MA. Premature release of data from clinical trials of ezetimide. *N Eng J Med* 2009;360:1455-1457; Letters to the Editor. The statins in preventive cardiology. *N Eng J Med* 2009;360:541-542; Couzin J. Cholesterol veers off script. In [31], *Science* 2008;322:220-223; Steinbergh D. The statins in preventive cardiology. *N Eng J Med* 2008;359:1426-1427.

[39] Kathiresan S. Lp(a) lipoprotein redux – From curious molecule to causal risk factor. *N Eng J Med* 2009;361:2573-2574; Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, et al. Genetic variants associated with Lp(a)N lipoprotein level and coronary disease. *N Eng J Med* 2009;362:2518-2528; Foulkes WD. Inherited susceptibility to common cancers. *N Eng J Med* 2009;359:2143-2153; Ledbetter DH. Cytogenetic technology - Genotype and phenotype. *N Eng J Med* 2009;359:1728-1730; Hoeijmakers. DNA damage, aging, and cancer. *N Eng J Med* 2009;361:1475-1501; Edelman E, Eng C. A practical guide to interpretation and clinical application of personal genomic screening. *Brit Med J* 2009;339:1136-1140; Veiraiyah A, Routledge PA. Effetti indesiderati degli anticoagulanti. *Adverse Drug Reaction Bulletin* 2009;191:765-768; Gazdar AF. Personalized medicine and inhibition of EGFR signaling in lung cancer. *N Eng J Med* 2009;361:1018-1020; Downward J. Finding the weakness in cancer. *N Eng J Med* 2009;361:922-

924; Bhatt DL. Tailoring antiplatelet therapy based on pharmacogenomics. *JAMA* 2009;302:896-897; Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009;302:849-858, Letters to the Editor. Adverse outcomes associated with use of proton pump inhibitors and clopidogrel. *JAMA* 2009;302:29-31; Thanassoulis G, O'Connell CJ. Mendelian randomization. Editorial. *JAMA* 2009;301:2386-2388; Hardy J, Singleton A. Current concepts; Genomewide association studies and human disease. *N Eng J Med* 2009;360:1759-1768; Ikram MA, Seshadri S, Bis JC, Fornage M, DeStefano AL, et al. Genomewide association studies of stroke. *N Eng J Med* 2009;360:1718-1728; Kraft P, Hunter DJ. Genetic risk prediction - Are we there yet?. *N Eng J Med* 2009;360:1701-1703; Hirschhorn JN. Genomewide association studies - Illuminating biological pathways. *N Eng J Med* 2009;360:1699-1701; Goldstein DB. Common genetic variation and human traits. *N Eng J Med* 2009;360:1696-1698; Woodcock J, Lesko LJ. Pharmacogenetics - Tailoring treatment for the outliers. *N Eng J Med* 2009;360:811-813; The Int Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical pharmacogenetics data. *N Eng J Med* 2009;360:753-764; Kohn DB, Candotti F. Gene therapy fulfilling its promise. *N Eng J Med* 2009;360:518-521; Yang JJ, Cheng C, Yang W, Pei D, Cao X, et al. Genome-wide interrogation of gemline genetic variation associated with treatment response in childhood acute lymphoblastic leukemia. *JAMA* 2009;301:393-403; Freedman JE, Hylek EM. Clopidogrel, genetics, and drug responsiveness. *N Eng J Med* 2009;360:411-413; Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Eng J Med* 2009;360:363-375; Mega JL, Close SL, Wiviott SD, Shen L, Hockrtt RD, et al. Cytochrome P-450 polymorphism and response to clopidogrel. *N Eng J Med* 2009;360:354-362; Sánchez-García I. The crossroads of oncogenesis and metastasis. *N Eng J Med* 2009;360:297-299; Attia J, Ioannidis JPA, Thakkistian A, McEvoy M, Scott RJ, et al. How to use an article about genetic association. *JAMA* 2009;301:191-197; Nakamura Y. Pharmacogenomics and drug toxicity. *N Eng J Med* 2008;359:856-858.

[40] Begley S. This is tour brain. *Aging*. *Newsweek* 2010; June 28 & July 5: 66-70; Carmichael M. Healthy at any age. *Newsweek* 2010; June 28 & July 5:54-65; Vegiopoulos A, Müller-Decker K, Strzoda D, Schmitt I, Chichelnitskiy E, et al. Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science* 2010;328:1158-1161; Ishibashi J, Seale P. Beige can be slimming. *Science* 2010;328:1113-1114; Begley S. Forget the cocaine vaccine. Low-tech treatments work better. *Newsweek* March 15, 2010, 22; Agre P, Leshner AI. Editorial. Bridging Science and Society. *Science* 2010;327:921; De Backer, Biston P, Devriendt J, Madl C, Chochrad D, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *New Eng J Med* 2010;362:779-789; Cicerone RJ. Editorial. Ensuring integrity of Science. *Science* 2010;327:624; Smith DP, King MT, Egger S, Berry MP, Stricker PD, et al. Quality of life three years after diagnosis of localized prostate cancer: population based cohort study. *Brit Med J* 2010;340:195-196; Eckel RH, Alberti KGMM, Grundy SM, Zimmet PZ. The metabolic syndrome. *The Lancet* 2010;375:181-183; Alberts B. Editorial. Promoting scientific standards. *Science* 2010;327:12; Reuben DB. Medical care for the final years of life. *JAMA* 2009;302:2686-2694; Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. *JAMA* 2009;302:2565-2572; Leshner AI, Turekian V. Editorial. Harmonizing global science. *Science* 2009;326:1459; Graf C, Battisti WP, Bridges D, Bruce-Winkler V, Conaty JM, et al. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. *Brit Med J* 2009;339:1299-1303; Letters to the Editor. Meaningful explanations vs scientific causality. *JAMA* 2009;302:2320-2321; Ludwig DS, Brownell KD. Public health action amid scientific uncertainty. *JAMA* 2009;302:434-435; Letters to the Editor. Clinical practice guidelines and scientific evidence. *JAMA* 2009;302:142-147; Helliman HE, Bedford HE. Bad science, risky medicine. *Brit Med J* 2009;338:1568; Brook RH. The science of heath care reform. *JAMA* 2009;301:2486-2487; Alberts

B. Editorial. On incentives for innovation. *Science* 2009;326:1163; Redberg RF, Walsh J. Pay now, benefits may follow – The case of cardiac computed tomographic angiography. *N Eng J Med* 2009;359:2309-2311; Schermerhorn M. A 66-year-old man with an abdominal aortic aneurysm; *JAMA* 2009;302:2015-2022; Lederle FA, Freischlag JA, Kyriakides TC, Padberg Jr FT, Matsumura JS, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm. *JAMA* 2009;302:1535-1542; Sipkins DA. Rendering the leukemia cell susceptible to attack. *N Eng J Med* 2009;361:1307-1309; Sanda MG, Kaplan ID. A 64-year-old man with low-risk prostate cancer. *JAMA* 2009;301:2141-2151; Hu JC, Gu X, Lipsitz SR, Barry MJ, D’Amico AV. et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA* 2009;L302.1557-1564; Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, et al. Outcomes of localized prostate cancer following conservative management. *JAMA* 2009;302:1202-1209; Moses III H. Researchers, funding, and priorities. *JAMA* 2009;302:1001-1002; Dubben H-H New methods to deal with publication bias. *Brit Med J* 2009;339:468-469; Khosla S. Increasing options for the treatment of osteoporosis. *N Eng J Med* 2009;361:818-819; Letters to the Editor. The importance of brown adipose tissue. *N Eng J Med* 2009;361:415-421; Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *The Lancet* 2009;374:86-89; Begley S. When studies collide. *Newsweek* June 29, 2009;22; Cheng TL, Jenkins RR. Health disparities across the lifespan. *JAMA* 2009;301:2491-2492; Sridharan L, Greenland P. Editorial policies and publication bias. *Arch Intern Med* 2009;169:1022-1023; Chew S. Adverse Drug reaction bulletin. Miopatia indotta da statine nell’anziano – Parte II. 2009;189:757-760; Harris JC. Toward restorative medicine – The science of care. *JAMA* 2009;301:1710-1712; Celi FS. Brown adipose tissue – When it pays to be inefficient. *N Eng J Med* 2009;360:1553-1556; Groves T. Managing research data for future use. *Brit Med J* 2009;338:729-730; Hall MA, Schulman KA. Ownership of medical information. *JAMA* 2009;301:1282-1284; Baerlocker MO, Detsky AS. Professional monopolies in medicine. *JAMA* 2009;301:858-860; Glickman SW, et al. Ethical and scientific implications of the globalization of clinical research. *N Eng J Med* 2009;360:816-823; Shojania KG, Levinson W. Clinicians in quality improvement. *JAMA* 2009;301:766-768; Kraemer JD, Gostin LO. Science, politics, and values. *JAMA* 2009;301:665-667; Ping P. Getting to the heart of proteinomics. *N Eng J Med* 2009;360:532-534, Tan JC, Chertow GM. Cautious optimism concerning longterm safety of kidney donation. *N Eng J Med* 2009;360:522-523; Editorial. A favourable (molecular) signal for personalized medicine. *The Lancet* 2009;373:2. Kelly CP, LaMont T. *Clostridium difficile* – More difficult than ever. *N Eng J Med* 2008;359:1932-1940; Hassan MHA. Editorial. Making one world of science. *Science* 2008;322:505.

[41] Mayor S. Researchers refine in vitro test that will reduce the risk of “first in humans” drug trials. *Brit Med J* 2009;338:11.

[42] Editorial. Phase 0 trials: a platform for drug development?. *The Lancet* 2009;374:176.

[43] Wynia MK, Ivey SL, Hasnain-Wynia R. Collection of data on patients’ race and ethnic group by physician practices. *N Eng J Med* 2010;362:846-850;

[44] Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *Brit Med J* 2009;339:144-147; Campbell M. What about absolute risks?. *Brit Med J* 2009;338:732; Avorn J. Drug warnings that can cause fits - Communicating risks in a data-poor environment. *N Eng J Med* 2008;359:991-994.

[45] Watts G. Beyond the impact factor. *Brit Med J* 2009;338:440-441.

[46] Barker R. A flexible blueprint for the future of drug development. *The Lancet* 2010;375:357-359.

[47] Rossini L, Rossini P. Pharmacotherapeutic receptor specificities and selectivity classes, and placebo effects: A perspective. *Pharmacologyonline* 2006;2:206-235; Walach H, Brailion A. Homoeopathic remedies and drug-regulatory authorities. *The Lancet* 2010;375:279-280; Kuehn BM. Despite health claims by manufacturers, little oversight for homeopathic products. *JAMA* 2009;302:1631-1634; Kaptchuk TK, Kerr CE, Zanger A. The art of medicine. Placebo controls, exorcisms, and the devil. *The Lancet* 2009;374:1234-1235; Nunn R. It's time to put the placebo out of our misery. *Brit Med J* 2009;338:1015.

[48] Letters to the Editor. Postherpetic neuralgia in herpes zoster. *JAMA* 2009;302:1862-1863; Freynhagen R, Bennett M. Diagnosis and management of neuropathic pain. *Brit Med J* 2009;339:391-395; Whitley RJ, A 70-year-old woman with shingles. *JAMA* 2009;302:73-80; Rossini L. Neuropatia post-erpetica nell' anziano: Un seminario. *New Entries Pharmacol* 2007;2:3-14.

[49] Bonati M. Farmaci essenziali per i bambini. *BiF* 2008;XV:45-48.

[50] Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry - sponsored trials of gabapentin for off-label use. *N Eng J Med* 2009;361:1963-1971; Landefeld CS, Steinman MA. The neurontin legacy – Marketing through misinformation and manipulation. *N Eng J Med* 2009;360:103-106.

[51] Mello MM, Studdert DM, Brennan TA. Shifting terrain in the regulation of off-label promotion of pharmaceuticals. *N Eng J Med* 2009;360:1557-1566.

[52] Llinares GJ, Head of Orphan Medicines, European Medicines Agency (Cf: Jordi.Llinares@ema.europa.eu): 178.2.2003 Commission Communication.pdf; gral guidance orphans.pdf; format_content_orphan_applications_rev3_200707.pdf; Regulation 141 2000.pdf; Regulation 847 2000.pdf; Lliang BA, Mackey T. Reforming off-label promotion to enhance orphan disease treatment. *Science* 2010;327:273-274; Mitka M. Off-label cancer drug compendia found outdated and incomplete. *JAMA* 2009;301:1645-1646; Rosenbaum L. Living unlabeled – Diagnosis and disorder. *N Eng J Med* 2008;359:1650-1653.

[53] Dombret H, Gardin C. An old AML drug revisited. *N Eng J Med* 2009;361:1301-1303; Boguski MS, Mandi KD, Sukhatme VP. Repurposing with a difference. *Science* 2009;324:1394-1395; Anderson T. Novartis under fire for accepting new reward for old drug. *The Lancet* 2009;373:1414.

[54] Cf.: European Medicines Agency (info@ema.europa.eu; www.ema.europa.eu) Monthly report, for example Issue n 1004, Pharmacovigilance Working Party (PhVWP) plenary meeting on 19-20 April 2010; Editorial. La via italiana agli studi post-marketing. *BiF* 2008;XV:145-146; Anonymous. Eudravigilance, Le segnalazioni spontanee trovano la loro rete. *BiF* 2006;XIII:26-27; Reazioni, Bollettino bimestrale farmacovigilanza AIFA; Farmacovigilanza News Newsletter AIFA (<http://aifa.progettoecce.it>); Psocare Project AIFA.

[55] Epstein RM, Korones DN, Quill TE. Withholding information from patients - When less is more. *N Eng J Med* 2010;362:380-381; Liang BA, Mackey T. Reforming off-label promotion enhance orphan disease treatment. *Science* 2010;327:273-274; Anonymous. Postmarket studies lag. *JAMA* 2009;302:2423; Editorial. The FDA's poor oversight of postmarketing studies. *The Lancet* 2009;374:1568; Barach P, Johnson JK. Variation in adverse events over the academic year. *Brit Med J* 2009;339:929-930; Steinbook R. Drug shortages and public health. *N Eng J Med*

2009;361:1525-1527; Avorn J, Schneeweiss S. Managing drug-risk information – What to do with all those new numbers. *N Eng J Med* 2009;361:647-649; Boguski MS, Mandi KD, Sukhatme VP. Repurposing with a difference. *Science* 2009;324:1394-1395; Rittenhlouse DR, Shortell SM. The patient-centered medical home. *JAMA* 2009;301:2038-2040; Letters to the Editor. Adverse events related to medication leading to hospitalization. *Arch Intern Med* 2009;169:810-811; de Heus R, Mol BW, Erwich J-JHM; van Geijn HP, Gyselaers WJ, et al. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. *Brit Med J* 2009;338:758-760; Jensen A, Sharif H, Fredericksen H, Krüger Kjaer S. Use of fertility drugs and risk of ovarian cancer: Danish population based cohort study. *Brit Med J* 2009;338:580-583; Webb PM. Fertility drugs and ovarian cancer. *Brit Med J*. 2009;338:551; Begley S. The depressing news about antidepressants. *Newsweek* February 8, 2010, 38-44; Editorial. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *Brit Med J* 2009;338:155-158; Kao DP. What can we learn from drug marketing efficiency? *Brit Med J* 2009;338:141-144.

[56] Vannugli R. Health Ministry Uff Rapp Intern 230/36.40/4.10.14, 14.8.91, to Mahler, General Director of WHO, Geneva. Delegation to participate in the WHO Adverse Drug Monitoring System of Centro Monitoraggio Farmaci, Istituto Medicina Sperimentale e Clinica, Università degli Studi di Ancona.

[57] 5th Meeting of the Representatives of National Centres participating in the WHO International Drug Monitoring Scheme, WHO-ITA / ITA-OMS, University of Ancona Medical School, Portonovo (AN), October 4/8, 1982.

[58] Rossini L, Bernardi M, Cavalieri L, Concettoni C, Galeazzi G, et al. Farmacovigilanza internazionale: Uso e abuso dei farmaci. Contribution of 21 June 1991, *Acc March Sci Lett Arti Ancona*. Memorie 1996;XXIX:151-198.

[59] Faculty Meeting of the Medical School, Università' di Ancona. Meeting of 11 May 1983, item 6: University / I.N.R.C.A. agreement for Pharmacology.

[60] Marche Regional Government, Decree of the Health Service Director no. 133/S04, 5. 12. 08, Re: Agreement as per art 1, para 819, Law 296/06, Marche Region /AIFA, to implement the Pharmacovigilance Project “Actions for the resumption of adverse reaction reporting in Marche” (Cf. I fondi regionali di farmacovigilanza. *BiF* 2008;XV, n 6. Insert pp 3-15); Authorization of the Board of Università Politecnica delle Marche, Faculty Meeting of the Medical School of 9 March 2010, with reference to Bando AIFA 2008, area B 2 “Valutazione degli eventi avversi dei mezzi di contrasto e dei radiofarmaci utilizzati a fini diagnostici e terapeutici”; Bernardi M, Bradu D, Di Sarra B, Galeazzi G, Marcucci M, Montecchiani G, Moretti V, Moroni L, Re L, Rossini L, Rossini P, Tonnini C. Ionic and non-ionic contrast agents. A contribution by WHO-ITA and The Drug Documentation and Information Centre of Regione Marche. *Pharmacologyonline Newsletter* 2010;3: this Volume. It may be appropriate here to mention the verdict of the Marche Administrative Tribunal of 4 May 2010, no 201/2010, as per appeal no. 1520/1994, and registered mail 02141-4, 23.6.2010 no. 136889356/13-7,14-8, 15-9 and 16-0: “In Ancona a University professor, one of its very founders, was prevented from achieving the “desire” (conscious, anthropogenic) of any living creature to constitute this being as an I, and to reveal it as such to himself and to others as self-consciousness, by way of his own work, free and historical intentional becoming, sought evolution, conscious progress in the necessarily multifarious reality of fundamental social relations. Essentially to be achieved with the risk of satisfying its acknowledgement via a life-or-death struggle of pure prestige of realization and revelation of his destiny. Of acquisition of experience through dialectic suppression of its immediately subordinated limitedness, making it a source of human progress in the social historical overcoming process. In

the anguish of the feeling of the power of perfection that can be achieved only in the execution, with staid work, of what has been planned. Free task of educating endeavour, capable of stability, taking permanent autonomy of spirit embodied in the real historical world of the objective history of being, finally directed at freeing him from the same existential anguish” (modified from A. Kojève, Commented translation of Section A of Chap IV of the Phenomenology of the Spirit, in “Introduzione alla lettura di Hegel”, Adelphi Ed, Milano, 2010, pp 17-44). Something that here was denied as if because of substantial inexistence.

[61] 6th SIF Interregional Meeting, Emilia-Romagna, Friuli-Venezia Giulia, Marche, Trentino-Alto Adige and Veneto, Portonovo (Ancona) 23 April, 1991. Introductory Address, and article, *Il Corriere Adriatico*, Ancona, “Pharmacology Today - Researchers Comparing Notes ...” “There is less and less justification for treating a patient on the basis of epidemiological studies and conventional small-sized, short-term therapeutic trials. Comparative studies need to be conducted for the various drugs in the various new and old therapeutic classes. In view of the possibly overwhelming and prohibitive costs of long-term ad hoc explorative-epidemiological studies, the alternative consists in analytical, systematic study by comprehensive observation of the very largest number of patient cohorts throughout informatics processing”.

[62] See: [58, 24, 14, 3]; Rossini L. Sul rilevamento degli effetti indesiderati da farmaci nella fase IV: Suggerimenti al medico pratico. *Fed Medica* 1985;8:92-97.

[63] Di Sarra B, Piantelli F, Moretti V, Re L, Rossini L, et al. Physio-pharmaco-toxicological in vivo read-out: An interuniversity integrated analytical center. Issues, results and perspectives. Volume for the 20th anniversary of Ancona University, and *Quad March* 1989;5:183-185.

[64] Mangano NG. Registri e rete nazionale di farmacovigilanza. *Reazioni* 2009;15:1; Anonymous. Rapporto OsMed 2008. Registri di monitoraggio dell’ AIFA. *BiF Online Special* 2009; Appendice A:254-259.

[65] Rossini L. Registrazione temporanea monitorizzata: Proposta di verifica. In *Nuovi Aspetti di Tossicologia Sperimentale e Clinica*. GC Edizioni Medico Scientifiche 1979:457-470;

[66] Rossini L, Leone L. Sviluppo del programma internazionale farmacovigilanza OMS nel nostro paese. *Rassegna Clinico Scientifica* 1977;LIII:1-19 (Documenti del lavoro OTA in corso al riferimento [10], pp 18-19).