Presidenza del Consiglio dei Ministri

ITALIAN NATIONAL BIOETHICS COMMITTEE

SECRECY IN DRUG REGULATORY SYSTEM PROCEDURES

28th of May 2010

INTRODUCTION

The document tackles the ethical issues concerning the secrecy of data in new drugs authorisation procedures and in the information about the drug's development after its introduction on the market. The regulatory authorities are sworn to secrecy due to European regulations and therefore they make public only summative documents about the documentation and the procedures on the basis of which a new drug is introduced on the market. The pharmaceutical industry believes it has the right to uphold the secrecy to avoid spreading information that could be useful to the competition, given the large capital they have to invest to develop a new drug.

After an analysis of the international and national legal framework of reference, the Italian NBC tackles the arguments of those who support the "secrecy" and the arguments in support of "transparency". The Committee believes that ethics demands the full availability of the data – with well-defined regulations – to scientific societies or patients and consumers associations, insofar as toxicological data and clinical studies are concerned, seen as the patients participate to the trials free of charge and with risk (even if limited). The availability of these data must be possible only after the procedures of authorisation or rejection have been completed. The NBC observes that the *Food and Drug Administration* publishes all the data whilst this does not happen with the European body EMA and consequently with all national agencies. The NBC hopes for an abolition of the secrecy so that the patients' interest can prevail over industrial interests.

The document has been elaborated by the working group coordinated by Prof. Silvio Garattini, with the contribution of Prof. Carlo Flamigni, Prof. Laura Guidoni, Prof. Assunta Morresi, Prof. Demetrio Neri, Prof. Andrea Nicolussi, Prof. Monica Toraldo. Doctor Sergio Dompé, President of the Farmindustry and Doctor Sergio Pecorelli, President of AIFA were consulted.

The document was unanimously approved by those present: Prof. Salvatore Amato, Prof. Luisella Battaglia, Prof. Adriano Bompiani, Prof. Stefano Canestrari, Prof. Roberto Colombo, Prof. Bruno Dallapiccola, Prof. Antonio Da Re, Prof. Lorenzo d'Avack, Prof. Maria Luisa Di Pietro, Prof. Riccardo Di Segni, Prof. Carlo Flamigni, Prof. Romano Forleo, Prof. Silvio Garattini, Prof. Marianna Gensabella, Prof. Aldo Isidori, Prof. Assunta Morresi, Prof. Andrea Nicolussi, Prof. Laura Palazzani, Prof. Vittorio Possenti, Prof. Lucetta Scaraffia, Prof. Monica Toraldo Di Francia, Prof. Giancarlo Umani Ronchi. Prof. Francesco D'Agostino and Doctor Laura Guidoni, absent from the meeting, expressed their agreement.

The President

Prof. Francesco Paolo Casavola

This opinion intends to discuss the ethical aspects raised by the secrecy of data in new drugs authorisation procedures as well as in the information regarding the phase following their introduction on the market. As it will be clarified later, the reason usually given to justify secrecy is to avoid damaging the pharmaceutical industry in its research for the manufacture of new drugs, giving the competition an unfair advantage by divulging particularly relevant data and information. This document however states that the argument of protecting private economic initiative and industrial monopoly must be not only adequately clarified in relation to its effective importance in justifying secrecy, but also integrated by other points of view that must be taken into account for a thorough bioethical evaluation of the issue. In other words, it is necessary to balance it with other relevant principles from both a specifically ethical perspective as well as constitutional values.

1. Framework of reference

First of all we must remember that private economic initiative is not a value that has absolute protection in the Italian Constitution, according to which it “must not be carried out against the common good or in a way that may harm public security, liberty, or human dignity” (art. 41 of the Constitution). This principle after all is in line with other fundamental guidelines of European market regulations, based on the principle of safeguarding consumers. In particular, we cannot forget the right to the protection of health, recognised in the Constitution as a basic right of the individual and in the public interest (art. 32 of the Constitution). This right forces us to avoid abuses that can favour the consumption of drugs whose therapeutic efficacy has not been adequately tested and verified. In addition, secrecy could be shown to be against the right of patients, both current and future, to be properly informed. From the point of view of public interest, secrecy must be compatible with the constitutional value of scientific and technical research (art. 9 of the Constitution), the promotion of which requires the dissemination of information and data concerning the procedures and outcomes of the tests. As we can see, these are principles that cannot be underestimated or sacrificed by allowing secrecy to extend beyond what is justified by the need of protecting someone’s ideas from being inappropriately commercially exploited by someone else.

We believe it is necessary to make available the information that can affect the health and well-being of the patients as well as that which is useful to the advancement of scientific knowledge.

2. The European regulatory system

The EMA (*European Medicines Agency)* is the European regulatory body, which uses its scientific technical body, the CHMP (*Committee on Human Medicinal Products*), to evaluate dossiers relative to new drugs. The

CHMP's assessment determines whether all European Union Countries must introduce the new drug on the market. The CHMP, made up of experts representing 27 Countries of the European Union, receives from the pharmaceutical industry the documentation relative to a new drug with regards to its quality, efficacy and safety. Each dossier is over a hundred volumes and is put together exclusively by the pharmaceutical industry. The dossier also includes the assessment of an external expert, who however is employed by the pharmaceutical industry and therefore does not guarantee an impartial judgement (1). In the same way, the documentation presented after the product's introduction on the market, with regards to dosage, toxic effects or to include new therapeutic instructions, comes exclusively from the pharmaceutical industry. If the dossier is the object of substantial criticism, the pharmaceutical industry can withdraw the request for approval in order to avoid receiving a negative answer. If the CHMP opposes the commercialisation of a drug, the company can appeal; but it is always the CHMP, not another committee, that re-examines the dossier even in "appeal".

3. What we know and what we don't know about approved drugs

In the case of a positive answer, the EMA announces it with a short press release. Then, together with the pharmaceutical company concerned, it draws up the EPAR (*European Public Assessment Report*, which summarises the product's characteristics and the methods with which its approval was decided), the SPC (*Summary of the Product Characteristics*, a technical file aimed at the prescribing doctor), and the instructions that are placed inside the packaging to inform the patients (2). Apart from these documents, which are made publicly available, the EMA and all its members – collaborators, consultants, including the members of the CHMP – are sworn to secrecy. It is therefore not possible to directly ascertain if the reasons for approving or rejecting a new drug are in line with the documentation provided by the pharmaceutical industry, because it is not possible to access the original documentation. Similarly, it is not possible to access the files for the collection of individual data on which the results presented by the pharmaceutical industry are based, because generally they are not even communicated to the EMA (3). Despite the improvements in transparency carried out by the EMA, it is still impossible to access the original documents or to know the opinion of the minority, should the CHMP's answer not be unanimous (3).

A different policy is followed by the United States' *Food and Drug Administration* (FDA), which makes available the data relative to all clinical research when they are requested for scientific reasons by groups of academics or by patients or consumers associations; in addition, it communicates the evaluation of the *Advisory Committee* members, who are consulted before elaborating the final opinion (3).

4. Reasons for secrecy

Why does European legislation call for secrecy with regards to EMA activities? Essentially, because it is influenced by the warnings deriving from the interests of the pharmaceutical industry represented in Europe by the EFPIA (*European Federation of Pharmaceutical Industries and Associations*).

The fundamental reason to uphold secrecy is to avoid damaging the intellectual property of the pharmaceutical industry that used considerable financial resources to develop a drug and have it approved. It is true that the pharmaceutical industry owns the patent, states the EFPIA, but divulging information relative to the data necessary to have it approved would still give an advantage to the competition and therefore it would damage industrial interest and in effect the profits. With lower profits, the pharmaceutical industry would not be able to invest in research in the same way and in the end the patients themselves would be disadvantaged, because there would be fewer products to cure their illnesses (4).

5. Reasons for transparency

This argument, seemingly reasonable, has however many weak points. The idea that research generated with private funds must remain exclusive property of the pharmaceutical industry can be contested for at least three reasons:

(i) The pharmaceutical industry largely draws from research funded by national and international public agencies. Without this primary research it would be much more difficult for the pharmaceutical industry to carry out independently all the research needed as the starting point to formulate development hypothesis for their products;

(ii) Phases 2 and 3 of the clinical research are accomplished only thanks to the availability of the patients, who free of charge agree to undergo clinical trials, often with a personal sacrifice and exposing themselves to the risks associated with having little knowledge of the new products;

(iii) In the majority of European States the use of pharmaceutical products is guaranteed by the national healthcare service or by public insurance. Without public funding few patients would be able to buy medicines, which often have prohibitive costs.

In essence it is clear that, in the development of its products, the pharmaceutical industry benefits from a lot of public help and therefore it is not the only source of the necessary resources; without public contribution the development of drugs would be much more onerous for the pharmaceutical industry.

With regards to the statement that abolishing secrecy would help the competition and damage those who study and produce new drugs, it is necessary to make some distinctions (2). Secrecy concerning the methods of synthesis and production of a drug can certainly be justified, in the same way as the protection of the data relative to the methodologies developed specifically to discover a certain drug must be preserved. However we don’t see why it is necessary to hide the methods with which the toxic potential of a drug has been studied at the pre-clinical level. For instance, the data about

the mutagenic, carcinogenic, embryo-toxic action as well as the effects on reproduction, on organ toxicity, etc. is information that must be available and verifiable by those - researcher or public interest representative – who have the right to examine the toxic characteristics of products which might be used by millions of patients. There are even less arguments to deny access to information relative to the clinical trials. These are the most important data, as they determine the approval or rejection of a drug. There are no real reasons to believe that the availability of this information can benefit the competition, as it is very unlikely that these data can be of any relevance in producing new drugs, especially if the information is made available after authorising the product. In addition, if all the information was made available, eventual damages and possible advantages would affect the whole of the pharmaceutical industry and in the end balance each other out. With regards to the damage to patients due to the reduced incentive to research, it is important to remember that the amount of resources the pharmaceutical industry allocates to research is about three times less than what is allocated to advertising. It can therefore be stated that abolishing secrecy in some aspects of industrial research would allow an improvement in research thanks to the possibility of evaluation and criticism by third parties, not involved with those who produce the data and examine them to decide their commercialisation. In addition, seen as the American pharmaceutical system (FDA) allows access to toxicological and clinical data, we don't understand why this is not compatible with the European system (EMA).

6. Clinical trials registers

Another area dominated by secrecy is the possibility of accessing the data relative to clinical trials currently taking place, to avoid on the one hand unnecessary duplications and on the other hand the publication only of the results favourable to the drugs being studied. At present, all drugs' clinical trials in Italy are listed in a national Register at the AIFA and a European Register of Clinical Trials (EudraCT). However, the Register can not even be accessed at the end of the trials and it does not record all the outcomes.

7. What must be changed

The NBC believes that some important changes are necessary to the European legislation, in line with the purposes of biomedical research, which must always be aimed at protecting patients (art. 2 Oviedo Convention) (5).

1. Experimental toxicology data and clinical studies results must be available for reasons of public interest when a drug is introduced on the market. Another body could be responsible for assessing the requests and authorisations to access the documentation available.
2. The activity of the EMA must be more transparent: the original documents, the supervisor's report, the discussion within the CHMP, the minority position should be made available. EPAR and SPC must be drawn up by the CHMP independently, without the influence of the pharmaceutical industry producing the drug. The

pharmaceutical industry's appeal in case of a negative answer should be assessed by a body independent of the CHMP.

3. Good progress has been made towards obtaining the registration of the protocols of the drugs' clinical trials. However there are still too many inaccessible registers and it becomes difficult to research current studies and those that have been completed. It would be useful for all registrations to be quickly collected in a global register, accessible to everyone and held by an international body like the WHO.
4. All scientific institutions should sign research contracts that do not forbid the publication of the results and guarantee the immediate communication of any health damaging collateral effects. Ethics Committees with the task of evaluating drugs' clinical trials should have the responsibility of checking such research contracts to ascertain that the studies are registered and all results are made public.

In conclusion, it is important that scientific institutions and consumers and patients associations are allowed to access all toxicological and clinical scientific data concerning drugs, through an external body that evaluates the requests and authorisations to access the data, so that patients' interests are favoured over industrial interests.

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