

Scientific-ethical evaluation of clinical studies

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ABSTRACT

A rather long and tortuous road leads from an original discovery of a novel mechanism and of a new molecular entity (NME) to a new drug or treatment. The clinical part of development is strictly regulated and it is the responsibility of ethics committees to protect the rights, safety and wellbeing

of human subjects involved in a clinical trial. It is explained in a concise manner through recent examples of multinational clinical trials evaluated by the Ethics Committee for Clinical Pharmacology, Hungary (ECCP), how that duty is done in real life at the level of initiation of clinical studies. ECCP is convinced that a clinical trial cannot be ethically acceptable if it is not based on high quality scientific background and is not correctly elaborated in all detail.

Key Words: *Clinical study; Drug development; Ethics; Multinational trials*

The introduction of new drugs is continuously awaited and expected by society for curing or treating diseases without existing treatment, i.e. where there is an unmet medical need. Academic teams of molecular biologists, medicinal chemists and pharmacologists contribute significantly to the knowledge base that leads to the identification of molecular targets of novel drugs, find possible biomarkers, or develop new screening methods. Drug candidates are also born in the academic world (1-3). That is not the end of the story though.

The development and launching of new drugs to market is the lifeblood of the pharmaceutical industry. Big European pharmaceutical companies spend more than 14% of their turnover on research and development projects, which is more than what is devoted to development by any other industry, including software and computer services, aerospace and defence or automobiles (4).

LITERATURE REVIEW

Drug development is a risky, lengthy and rather expensive process. Only about 12% of the development programs lead to a new product, whereas almost 90% of those fail. Putting a new molecular entity (NME) to the market requires about 2.5 billion dollars of investment and 10-12 years of development time (5). The cost of development has been constantly increasing; and with the limited patent protection time it is vital for the sponsor that development should go the fastest way possible. Why do clinical studies fail? About 40% of the investigational products fail in phase I and 64% of those entering phase II cannot continue in phase III (5). By far the most important reason of failure in phase II is lack of efficacy at the maximum tolerated dose (6).

REGISTRATION TRENDS OF NEW DRUGS

The number of new drugs registered yearly by the FDA decreased from 59 in 1996 to 18 in 2007 (7). Clearly this trend looked rather gloomy for the industry and also for the patients suffering from various diseases with no suitable treatment. The disappointing trend apparently changed though and by 2016 the number of new drugs reached 45 (7). Different analysts gave different explanations of these simple facts. Initiatives of the FDA (8) and the EU, like the Innovative Medicine Initiative (9), might certainly help solving the problem. The discussion of these goes far beyond the topic of this paper and beyond my expertise as well. I want to focus on the issues that are, at least partly, originating from pressure on sponsors to get each development phase completed in the least amount of time possible and start the next phase as soon as possible. I believe that the advancement of life sciences gave a fresh start to pharmaceutical development in the second decade of the 21st century through the discovery and use of new targets such as members of signal transduction pathways, and via the application of principles and technology of molecular immunology, including production of fully humanized

monoclonal antibodies. An accelerated exchange of information between biological laboratory and clinics is catalyzed by translational medicine.

PHASES OF DRUG DEVELOPMENT

Entering the clinical phase of drug development means a different and more complex environment. In contrast to the discovery phase, this part is strictly regulated. Projects should be evaluated at each step from scientific as well as ethical points of view. Clinical development is divided into different phases: Phase I is designed for determination of the tolerance and pharmacokinetic properties of the investigational product in humans, usually involving healthy volunteers, or in special cases, patients. Phase II is the first real opportunity to show the efficacy and side effects of the investigational product in the targeted patient population, and it also aims at determining the dose to be used in further, larger studies. Phase II clinical studies usually involve around 100 patients. Phase III trials are in general large scale, multinational, multisite studies; and the number of patients can be several thousand. The efficacy and safety of the drug in development is studied in clinical Phase III. The registration of a new drug is based on the results of those studies. Once a drug is registered and is already on the market, the authorities may require further studies in order to learn more about the long-term safety of the new drug. Post marketing clinical trials are called Phase IV studies.

The sponsor may only start a clinical trial if the competent Ethics Committee has issued a favorable opinion and the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance (10).

Before the NME is first administered to humans, data should be reliably presented to the competent authority concerning the structure, quality and manufacturing details of the material. Its effects in preclinical models of the disease, both *in vitro* and *in vivo* should be demonstrated. If possible, the molecular mechanism of action should be described as well, including the molecular target and its role in the disease in question. Pharmacokinetic studies should prove that the target can be affected *in vivo*. Dose-response studies are also needed. Side effects (at least on vital organs) and at least preliminary animal toxicology should support the decision that the investigational product can be administered to humans. The first administration should take place at the dose selected on the basis of nonclinical experiments using the route of administration chosen. The clinical protocol should be ready in all details. According to the Oviedo Convention (11) and the Helsinki declaration (12) all participants in clinical studies should be properly informed about the interventions they are facing and can only be involved if they give their consent to those freely. At this point the Ethics Committees have their responsibility.

ETHICS COMMITTEES

Directive 2001/20/EC defines 'ethics committee' as: *an independent body in*

Ethics Committee for Clinical Pharmacology, Medical Research Council, Hungary

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a Member State, consisting of healthcare professionals and non-medical members. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data (10). Their role is defined in the Declaration of Helsinki: "(The ethics committee) must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects" (12).

Clinical trials can only be given the green light by the competent authority if the trial got a positive opinion from the ethics committee. The organization and the regulations of the ethics committees are member state competences in Europe. The number and composition of the ethics committees varies among the European member states. They may work in slightly different manner according to the local rules and traditions but the basic principles are of course identical (13). The European Network of Research Ethics Committees (EUREC) assists in the harmonization of the multidisciplinary ethical reviews (14). A notable difference is observed in the evaluation of the materials related to the informed consent process in case of clinical trials on medicinal products conducted with minors (15).

In some European countries several ethics committees (up to 215 in Belgium) share the responsibility. There is only one ethics committee in Hungary, which evaluates single- and multisite clinical trial protocols involving medicinal investigational products, with the exception of non-interventional trials. It is called Ethics Committee for Clinical Pharmacology (ECCP). In the following I confine myself to certain aspects of the Hungarian experience.

HUNGARIAN EXPERIENCE

The Committee has 30 members (24 medical doctors and 6 lay members who are in one way or other connected to healthcare and drug development) convening once every week with the participation of all members or a fraction of them. We receive about 350 new applications and more than 1500 requests for modification of the running studies a year. New applications are always discussed in plenary sessions. The focus of the Committee's attention is patient safety, the risk/benefit balance of the treatment. According to Article 6 of DIRECTIVE 2001/20/EC, the protocol, the suitability of the investigator and supporting staff, the investigator's brochure, and the quality of the facilities are also all evaluated. The documentation prepared for the informed consent procedure needs to be written in Hungarian and the contents must correspond to the above Directive as well as the local laws and rules, which are more detailed. The privacy of research subjects is also safeguarded by the ECCP. It is very clear that each protocol receives individual analysis, and patient materials can only be properly evaluated in relation to the clinical protocol itself. Further details of the working methods of ECCP are described in previous study (16).

In case some aspect of the documentation does not meet the requirements, the secretary of the Committee contacts the sponsor or their representative calling for rectification of the deficiencies according to the resolution of the meeting. ECCP much prefers improvements over rejection, since we are convinced that clinical trials and in general development of new drugs is beneficial to the patients participating and advances medical science as well. Our record of the last six years shows that the proportion of the rejected protocols is between 4.4% and 8.9% (Table 1).

TABLE 1

Clinical trial protocols evaluated by the Ethics Committee for Clinical Pharmacology, Hungary

Year	Protocols evaluated	Protocols without favorable opinion
2012	390	4.6%
2013	355	5.6%
2014	379	7.4%
2015	359	4.4%
2016	372	5.1%
2017*	325	8.9%

Only original submissions are introduced in the Table (i.e. modifications are excluded). *Year 2017 figures correspond to end of November 2017.

Now I wish to elaborate on the following question: for what reasons may a clinical study receive a non-favorable opinion from the Ethics Committee for Clinical Pharmacology, Hungary?

Many of the protocols when submitted are suffering from deficiencies in the patient materials. These originate from lack of consideration of the country specific requirements in the belief that master copies if correctly translated remain acceptable. Local laws and regulations, however, should be respected. A single letter of deficiency is usually well accepted by the sponsor and the changes required by the Committee are introduced until deadline. Some principal investigators (PI) and/or facilities do not meet the standards set by the law or the Committee may judge that conducting the study under their guidance or at those sites may present risk to the patients. NME's influencing signal transduction pathways, like tyrosine kinase inhibitors or monoclonal antibodies against certain protein components of the immune system may require special experience from the PI and his/her team. Some PI's and sites may therefore be excluded from the study until the necessary improvements are achieved but the trial still can start with other PI's selected by the sponsor. All those protocols can receive a favorable opinion from the ECCP after correcting the deficiencies.

Real issues emerge if ECCP judges that a multinational multicenter trial is submitted whose protocol either is a) not based on sound scientific results and assumptions, or b) it may represent unnecessary risk to all or some of the subjects. These cases are fortunately rare, but for resolving the problems the protocol needs to be modified, which is not straightforward and may present real difficulties to the sponsor.

Case a) usually derives from the time pressure mentioned under the second subtitle of this paper. The sponsor wishes to get support to the protocol without completing necessary nonclinical studies or clinical trials of a previous phase, e.g. submits a phase III protocol before the optimal dose would be determined in phase II. Results of nonclinical studies can be deemed non-reliable if only internal company reports describe them, or contradictory literature data are not considered. Value of certain animal models of disease may also be questioned as the sole basis of a first in human trial.

For case b) the patient selection criteria may be too loose, permitting inclusion of patients who are prone to serious side effects of the study drug or for whom a suitable alternative treatment is available. Also, too long use of placebo or ineffective comparator determined in the protocol is considered non-acceptable. In phase I, especially when radically novel approaches are introduced, subject dosing and dose escalation should be done with special care in order to avoid tragedies similar to what happened in London, or more recently in Rennes (17,18).

A third category of protocols that do not receive a favorable opinion is when the sponsor decides for any reason to withdraw it before a final decision is reached by the ECCP.

DISCUSSION

Outlook

Regulation 536/2014 of the European Parliament and of the Council (19) already in force shall apply six month after the so-called European Portal has achieved full functionality. That is expected in about a year from now. The Regulation describes in detail each and every step of the authorization procedure to follow for any clinical trial with medicinal products in the EU. Deadlines are also strictly regulated and they will be short. In case the reporting member state or the ethics committee of a state concerned does not raise objection to the trial within the deadline, the sponsor may start the trial in that member state. On the other hand, if the sponsor does not provide the requested additional information within the period set by the Member State concerned, the application shall be deemed to have lapsed in that Member State.

CONCLUSION

It is advisable therefore that all submitted material should be very carefully prepared, since, as the "General principle" set forth in Article 3 of the Regulation goes: "A clinical trial may be conducted only if:

(a) The rights, safety, dignity and well-being of subjects are protected and prevail over all other interests.

(b) It is designed to generate reliable and robust data." Competent authorities and ethic committees will both oversee the realization of that principle.

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