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Value of Post-Registration Studies for Reimbursement Renewal

Mathieu Molimard[1], *Marion Bamberger*[2], *Muriel Vray*[3] *and the participants in Round Table N°6, Giens XXIV*[⋆]

1 Département de Pharmacologie, CHU de Bordeaux, Bordeaux, France

2 Laboratoire Bristol Myers Squibb, Rueil-Malmaison, France

3 Unité d'Épidémiologie des Maladies Émergentes, Institut Pasteur, Paris, France

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Abstract – Post-registration studies describe parameters of real-life clinical practice such as the treated population, conditions of treatment initiation, treatment duration, adherence, associated benefits/risks as well as the impact on treatment strategies, healthcare procedures and on public health. The results of these studies are used in particular for re-evaluation, re-registration or in applications for reimbursement. Since 1997, 134 requests for post-registration studies have been made either by the French Transparency Committee (CT) and/or the Committee for Pricing of Healthcare Products (CEPS) and the results of these studies were taken into account in the re-evaluation of Actual Benefit (AB) or Improvement in Actual Benefit (IAB). During the roundtable discussion on this subject at the National Clinical Pharmacology Meeting held at Giens (France), the difficulties in performing such studies were identified and proposals were made to predict and anticipate requests for these studies but also for the training of physicians.

1. Introduction

The effects of drugs should be assessed throughout their lifecycle. Assessment begins by measuring pharmacological effects during preclinical studies and continues with the evaluation of clinical effects and the benefit-risk ratio until first registration on the Social Security reimbursement list and then during post-registration studies to provide measurements of efficacy in real-life clinical practice for successive reimbursement renewals. The purpose of post-registration studies is to describe in a real-life setting the conditions of treatment initiation, the treated population, treatment duration, adherence, associated benefits/risks as well as the impact on treatment strategies, healthcare and the impact on public health. The results of these studies are used in particular for re-evaluation, re-registration or in applications for reimbursement.

2. Nature of the request

For certain drugs, a request is made for a post-registration study at the time of their inclusion on the reimbursement list.

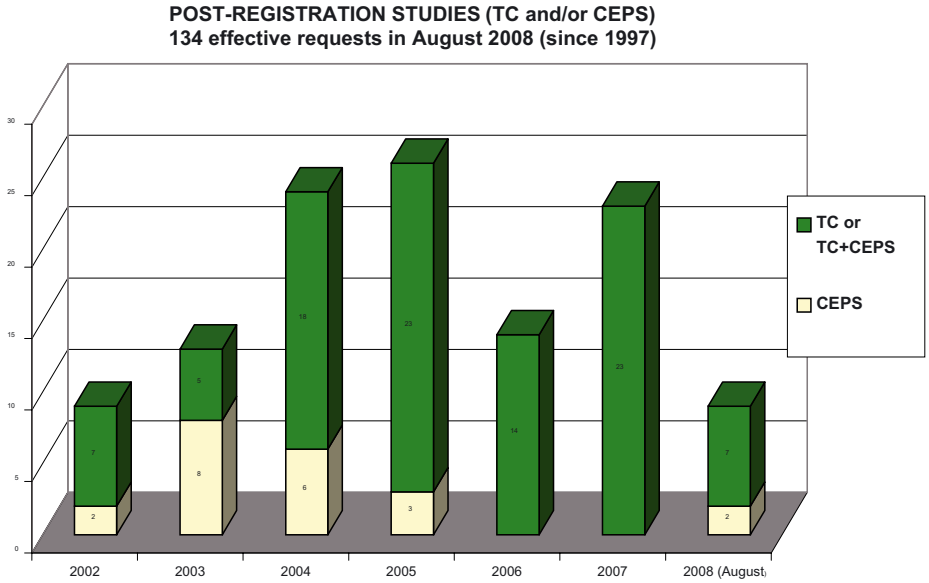
This is because only a limited amount of clinical trial data is available for evaluation by the Transparency Committee. By definition, these trials were performed under specific conditions and on particular patient populations. This information must therefore be completed and its transposability to real-life clinical practice studied.

The information provided by these studies helps the Committee reassess the Actual Benefit (AB), Improvement in Actual Benefit (IAB) and the reimbursement conditions of the product.

These studies are requested mainly by the Transparency Committee (TC) but they may also be demanded by the Ministry of Health [General Directorate of Health (DGS) and the Social Security Directorate (DSS) and the Committee for Pricing of Health Products (CEPS)]. Study requests and their objectives are noted in the TC opinion and are reproduced in the financial agreement signed by the company and CEPS when fixing the price according to the framework agreement signed between CEPS and Leem (Les entrepises du médicament).

In order to mutualize and harmonize requests, a liaison committee was set up in order to bring together the various partners concerned by these studies [DGS, DSS, HAS (Haute Autorité de santé), Afssaps (Agence française de sécurité sanitaire des produits de santé), CEPS, INVS (French Health Watch

⋆ For a list of participants, see the end of the article.



TC: Transparency Commission (Commission de la Transparence); **CEPS** : Comité Economique des Produits de Santé

Fig. 1. Number of actual requests for post-registration studies at the end of August 2008.

Institute), CNAMTS (Caisse Nationale d'Assurance Maladie des Travailleurs Salarié), etc.]. In parallel, there is a technical coordinating committee between HAS and Afssaps in order to study any common ground between the requested post-registration study and any study demanded by a European Risk Management Plan (RMP) or by Afssaps.

The follow-up of study requests and their set-up is ensured by HAS, which has a "one-stop shop" role. The company must then conduct the requested post-registration study after initially forming a scientific committee which is responsible in particular for drafting the protocol and conducting the study. The composition of the scientific committee and the draft protocol are submitted to the TC for validation. The Committee, through its "Public Health Benefit (PHB)" working panel, delivers an opinion on the composition of the scientific committee and the suitability of the protocol proposed after the initial study request. Several versions of the protocol are sometimes necessary before a favorable opinion is obtained.

The study is then set up by the pharmaceutical company. Its duration is variable from several months to several years. Once the study is completed, the results are submitted to the TC, in the form of a report which is analyzed by the PHB Group. The Committee is provided with a summary of the results which it will integrate in its opinion and will draw the necessary conclusions.

From 1997 (date of the first requests) to the end of August 2008, 134 effective study requests were made by the TC and/or CEPS (figure 1). These requests concerned 105 different proprietary drugs marketed by 49 companies. One product was concerned by a single request in 85% of cases. When there were several requests per product, these generally concerned different indications. The laboratories had to perform only one or two studies in 63% of cases and more than 4 studies in 18% of cases.

These requests concerned products with IAB I, II and III in 59% of cases and products with no IAB (level V) in 23% of cases. The products concerned had a high AB in 85% of cases.

These study requests concerned proprietary drugs in many different therapeutic classes, but nearly two thirds (63%) of requests concerned four classes: antineoplastic agents, anti-infective agents, central nervous system drugs and hormonal agents (except sex hormone). For five therapeutic classes or drugs in the same therapeutic category, post-registration studies were requested for all products: ß interferons, pituitary growth hormones, biotherapies in rheumatology and dermatology and medications for age-related macular degeneration (ARMD).

The parameters studied may be divided into four main categories: conditions of prescription and use (97% of requests), benefit for the patient (80% of requests), safety in routine clinical practice and its impact on treatment (58% of requests) and impact of treatment on the healthcare system (21% of requests). Most studies investigated several parameters. 77% of studies were asked to investigate conditions of use and benefit and 12% all four categories.

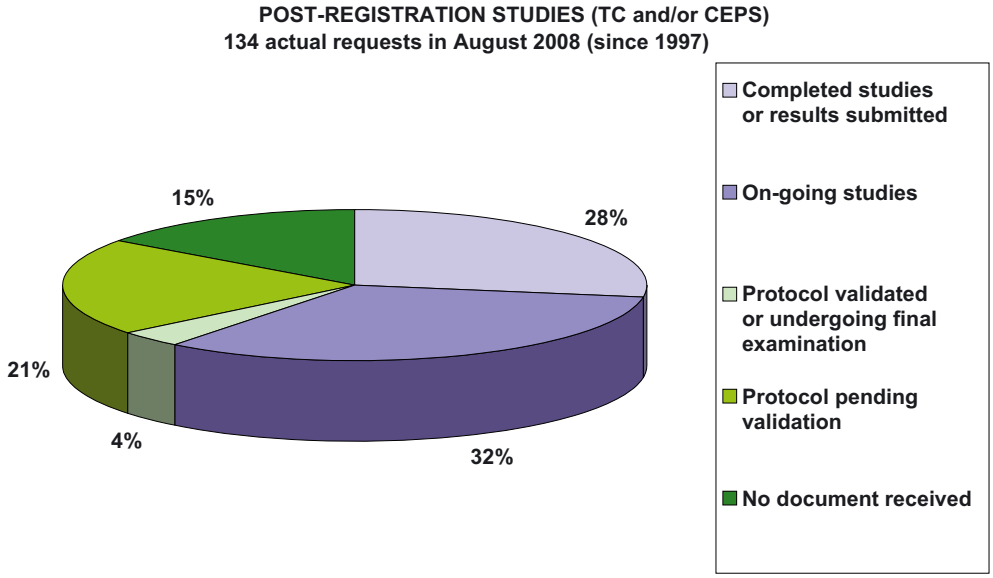


Fig. 2. Status of effective requests for post-registration studies at the end of August 2008.

At the end of August 2008, no protocol had been submitted for 20 out of 134 study requests (15%) including 8 recent requests (<10 months).

In parallel, a protocol had been submitted for 110 requests (85%) including: 28 (21%) pending validation of the protocol, 5 (4%) with a validated protocol (the study was about to start), 44 (32%) on-going studies and 37 (28%) studies for which the interim or final results had been submitted (including 57% of final results) (figure 2).

The many impacts of these studies are summarized in table I.

3. Difficulties encountered and proposed solutions

Several difficulties in performing these studies were identified and solutions proposed during the roundtable:

3.1. Difficulties with the request

There were sometimes difficulties in understanding the formulation of the objective of the requested study. This misunderstanding may lead to the proposal of inappropriate studies and therefore justifies setting up a procedure for clarification and accompanying the request. To improve comprehension, it is proposed that an appendix justifying the study request is included in the TC opinion. This appendix will also help explain the reasons why the study is required to the parent company. In addition, once the TC opinion has been validated, it should be made possible to rapidly contact the public health benefit group in order to clarify the objective.

The existence of similar requests from various European member states may also raise difficulties in the choice of study methods. Multiple national requests are already coordinated between the different requestors within the scope of the Liaison and Coordination Committee. A structure to coordinate requests from various member states would be useful.

3.2. Difficulties in financing

The cost of these studies must be anticipated by parent companies. This involves a better understanding of why the study is needed.

The understanding of this need and anticipation of the financial demands by parent companies may be improved by appending the rationale for the study to the transparency committee opinion and by an improvement in the foreseeability of these studies which are generally required for products: (i) that are truly innovative; (ii) have a broad target population; (iii) are evaluated on an intermediate endpoint; (iv) have a risk of misuse (MA [Marketing Authorization], reimbursement); (v) a problem of transposability (target populations, conditions of use, adherence, etc.).

In addition, the publication of the minutes of this roundtable discussion in English in Thérapie will improve communication on the needs of French subsidiary companies in this field to parent companies.

With regard to joint requests to several companies, although this may appear to be a simplification, it often leads to additional delays in order to obtain the agreement of all partners.

Table I. Impact of studies.

Institution concerned	Impacted marker
Afssaps/EMEA	MA and benefit/risk
	Pharmacovigilance/risk management plan
	Use and benefit-risk management, conditions of prescription and supply
	Guidelines
HAS:	AB
- TC	IAB
- CEESP	Target population
	Public health benefit
	Use and benefit-risk management/good drug use forms
	Guidelines
	Health economic evaluation
CEPS/Minister/DGS	Reimbursement
	Price (price volume agreements and other procedures)
	Public health benefit
Hospitals	Choice of drugs by the Medicinal Products Committee
Complementary and national health insurance	Efficacy
Regional health agencies	Good drug use agreements
	Individual contracts with doctors
	Contracts of objectives and good drug use

Afssaps: Agence française de sécurité sanitaire des produits de santé; **EMEA**: European Medicines Agency; **HAS**: Haute Autorité de Santé; **CEESP**: Commission d'Évaluation Économique et de Santé Publique; **CEPS**: Comité Économique des Produits de Santé; **DGS**: Direction Générale de la Santé; **MA**: Marketing Authorization; **SMR**: Service Médical Rendu; **ASMR**: Amélioration du Service Médical Rendu.

Finally, the cost of studies may be high with respect to forecast sales so that funding must be anticipated in every case. If the budget for the study is disproportionally high with respect to forecast sales, the possibility of deducting a discount may already be discussed in the agreement with CEPS. Financing would be improved if these studies were anticipated by companies. The setting-up of access to databases would also make it possible to reduce costs but few databases are accessible. Access to the health insurance databases should be possible for pharmaceutical companies and the creation of a database on the model of the English General Practice Research Database (GPRD) could be very useful.

3.3. Difficulties of realization and timeframe

Probably because these requests are relatively recent, they are rarely anticipated in the product development plan and this causes a delay between the study request and the submission of the first protocol. This time may be shortened by better communication of the request and early contact to clarify objectives and valorizing the time of the temporary authorization of use (ATU).

Submission to the Committee for the Protection of Persons within the scope of observational studies was strongly opposed as it induces additional delays and because these committees have no training in pharmacoepidemiology. As these studies are based on measuring the use of the drug in real-life practice the simple demand by these committees for the signature of a consent form would be a major source of bias reducing the validity of the case. Situations requiring an intervention (laboratory test, quality-of-life questionnaire, etc.) are rare.

The design of these studies is relatively poorly understood by medical teams who are more accustomed to performing clinical development. Adaptation to this type of study requires the acquisition of new skills. Methods must be adjusted to answer the questions asked. There is no existing scientific guideline to help choose or validate a particular design. It was proposed to set up training workshops based on practical examples.

The participation of physicians and patients in this type of study is difficult in particular because of ignorance of the need and value of these studies. Physicians' awareness of pharmacoepidemiology must be improved during their initial and continuing medical training, and learned societies must be involved in these studies (without them being obligatorily the effectors) and physicians must be informed of their results and conclusions. The description of the results in Transparency Committee opinions would allow public communication of the results, in particular to physicians.

4. Conclusion

This round table discussion showed that requested post-registration studies are carried out and the results are taken into

account in the reassessment of AB and IAB by the French Transparency Committee and CEPS. They improve knowledge on drug use in routine clinical practice. Difficulties have been identified and proposals made concerning communication of the request, the foreseeability of the requests, the costs of studies and training of physicians.

Participants

Marie-Pierre Allicar (GlaxoSmithKline), Véronique Ameye (Novartis), Bernard Avouac (Hôpital Henri Mondor, Créteil), Marie-Noëlle Banzet (Laboratoires Servier), Laurent Becquemont (Hôpital Bicêtre, Le Kremlin Bicêtre), Patrick Blin (Université Victor Segalen Bordeaux 2, Bordeaux), Corinne Duguay (Sanofi Aventis), Francis Fagnani (CEMKA), Danièle Girault (Wyeth Pharmaceuticals), Muriel Haim (MSD Chibret), Françoise Hamers (Haute Autorité de Santé), Olivier Lalaude (MSD Chibret), Véronique Lamarque (Laboratoire Pfizer), Patricia Maillere (IRIS groupe Servier), Jacques Massol (Hôpital Saint Jacques, Besançon), Philippe Maugendre (Haute Autorité de Santé), Arlette Meyer (Direction Générale de la Santé), Thierry Moreau-Defarges (Laboratoire Janssen-Cilag), Atul Pathak (Pharmacologie Clinique, Faculté de Médecine, Toulouse), Anne Perillat (Direction Générale de la Santé), Sophie Ravoire (Laboratoire Lilly), Alain Spriet (Consultant), Sophie Tardieu (AP-HM, Marseille), Bernard Teisseire (CEPS, Ministère de la Santé et des Sports, Paris), Monique Weber (CNAMTS), Laura Zanetti (Afssaps).

Correspondence and offprints: *Mathieu Molimard*, Département de Pharmacologie, CHU Pellegrin Carreire, 33076 Bordeaux Cedex, France.
E-mail: mathieu.molimard@pharmaco.u-bordeaux2.fr

