

Postmarketing Evaluation of Drugs

Actual Efficacy, Population Exposed and Impact on Public Health

Catherine Le Galès,¹ Abdelkader El Hasnaoui,² Jean-Marie Goehrs³ and the Participants in Round Table No. 2, Giens XVIII[†]*

1 INSERM U537/DGS, Paris, France

2 Laboratoire GlaxoSmithKline, Marly-le-Roi, France

3 Laboratoire MSD, Paris, France

Abstract

Round table no. 2 was devoted to the postmarketing evaluation of drugs. The debates involved both the questions posed by postmarketing evaluation and the methods for responding to them. The major categories of questions likely to be posed are as follows: efficacy in actual situations; safety in actual situations; prognostic factors and patients responding; place in the therapeutic strategy; impact on the healthcare care system; the 'joined' population (those who actually obtain benefit); and drug utilisation review. In addition, the methodological approaches have been divided into three categories: the experimental approach, the observational approach and the modelling approach. Each of these methodological approaches has been qualified with respect to each of the questions. The objective was neither to establish a classification of the methods according to the level of proof, nor to propose methodological formulae. Instead, the participants applied themselves to describe the strengths and the limits of the different methods for each of the questions in turn. The debates then focused on the process of identification of pertinent questions and appropriate methods. In this context, the round-table participants applied an analysis of the current system of postmarketing study projects and formulated some propositions for their improvement. Finally, the place of existing databases in the postmarketing evaluation was discussed and the participants emphasised the importance of initiating a very detailed assessment of the information that could be provided by such databases before instituting *ad hoc* studies.

Keywords: evaluation, commercialisation, drugs, efficacy, population exposed, public health

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1. Introduction: Scope of the Considerations

The French system of entering a drug on the reimbursement list and fixing its price arises from a process that can be divided into three steps: a marketing authorisation (autorisation de mise sur le marché [AMM]) awarded increasingly commonly at the European level; the potential entering of the product on the list of reimbursable specialities and the fixing of its level of reimbursement according to an opinion of the Transparency Commission intended for the ministers in charge of Health and Social Security; and the fixing of the selling price of the product to the public based on proposals of the Economic Committee of Health Products (Comité Economique des Produits de Santé [CEPS]).

This process is now well established. However, during the last 2 years, several events have led to an emphasis in this system on the evaluation of the benefit to public health of a drug.

First, the decree of October 27, 1999,^[1] clarified the criteria of assessment of medical service rendered usually employed by the Transparency Commission: efficacy; undesirable effects of the drug; severity of the condition treated; place in the therapeutic strategy; the existence of therapeutic alternatives; and whether the drug effect is preventive, curative or symptomatic. The decree also introduced a new criterion: the benefit to public health (l'intérêt de santé publique [ISP]). This decree constitutes the juridical basis for the evaluation process.

[†] For a list of participants, please see the end of the article.

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The second event is the mission letter sent by the Minister of Social Affairs in July 2001 to the CEPS. This letter raised the possibility of including a programme of postmarketing studies in the conditions of admission to the reimbursement list of some products, and this has to be included in the conventional context linking the state to the pharmaceutical companies.

The mission statement sent in June 2001 to the president of the national monitoring system for the prescription and use of drugs in outpatient and hospital sectors (Observatoire National des prescriptions et consommations des médicaments dans les secteurs ambulatoires et hospitaliers) set out, in a complementary fashion, some of the conditions of this postmarketing study programme. The monitoring system is entrusted with the mission of participating in the follow-up of postmarketing studies especially ensuring, at the request of the Transparency Commission or the CEPS, the methodological validation of the prepared protocols.

Finally, in January 2002, in order to better assess the ISP of a drug during decisions involving entry into the reimbursement and price-fixing processes, the Directorate-General of Health (DGS) was eager to define this criterion and the method of assessing it by incorporating, in this assessment, public health priorities and the politics associated with health and the organisation of the healthcare system.

In this context, it was decided that the ISP of a drug should be evaluated by means of its impact on the state of health of the population: a drug is awarded an ISP if it is able to improve, directly or indirectly, the state of health of the population. A pertinent, pragmatic and realistic evaluation of the ISP of a drug should therefore be based on data that take account of actual practice, be subject to periodic revision, and be documented according to the criteria considered in any intervention in public health, and more especially the following:

- the impact on the state of health of the population in terms of mortality, morbidity and/or quality of life;
- the impact on the healthcare system, which is based specifically on the ability to identify and reach the target population.

It was in this largely renewed and very productive context that, in October 2002, the Giens XVIII round table no. 2 was held, and dedicated to the postmarketing evaluation of drugs, i.e. actual efficacy, population exposed, and impact on public health. The debates dealt with the following questions as a priority:

1. What are the main questions posed by the postmarketing evaluation of a drug and what are the main methodological approaches used to respond to them (figure 1)?

2. Once the questions and methods were listed, the debates turned to the process of identification of the pertinent questions and appropriate methods. In this context, what analysis did the

Postmarketing studies	
What is involved?	
Pharmacoepidemiological studies	Marketing studies
Observational studies	Phases IV
ISP studies	Phases IIIb
Cohort follow-up studies	Investigational
Morbidity/mortality studies	Observational
Pharmacovigilance studies	
Impact studies	Pragmatic studies

Fig. 1. Different studies denoted by the term 'postmarketing'. ISP (intérêt de santé publique) studies are those that benefit public health.

round-table participants make of the current system of post-AMM study projects and what suggestions were made for their improvement?

3. What is the place of existing databases during the definition and execution of these study projects?

2. Methodology

With regard to the questions posed in the context of evaluating the ISP and the ways that could be used to respond to them, the methodological approach has been divided into two stages. Initially, the major categories of questions likely to be asked downstream of the marketing of drugs have been listed as well as the main methodological approaches. This is followed by the construction of a matrix of Questions/Methodological approaches. The objective of this matrix was not to attempt a classification of the methods according to the level of proof, or to propose 'methodological recipes' but rather to describe the strengths and limits of the different methods when they are used to reply to different questions.

In this context, a glossary consisting of a definition of the main concepts has been developed:

- *Experimental approach:* In medical research, the experimental approach consists of initiating an intervention (for example administration of a treatment) in the context of a protocol, with the aim of measuring the effect. The experimental character involves different aspects of the implementation and in particular a selection based on precise criteria of the people who will benefit from the intervention.
- *Observational approach:* This approach consists of the naturalistic observation of health events without influencing them (exposure to a risk factor, administration of a treatment, incidence of a condition etc.), with the aim of either describing the modalities, or measuring the effect.

- *Modelling approach*: In the absence of any experimental or observational data, a health event or an intervention will be simulated on the basis of a mathematical model in order to estimate the effects.
- *Efficacy in an actual situation*: This describes the efficacy of a drug in its 'joined' population (those who actually obtain benefit) and under actual conditions of use by patients.
- *Safety in an actual situation*: This describes the safety of the drug in its 'joined' population and under the actual conditions of use by patients. In addition, the expanded use of the drug after marketing offers the possibility of studying rare adverse effects.
- *Prognostic factors*: Prognostic factors are those with a link to the onset of the condition. These can in some cases affect the safety and efficacy of the drug.
- *Impact on the health system*: This can be defined as the expected changes or changes produced by the prescription of a drug in medical practice and the use of the health services by the people concerned. Documentation of the impact on the health system supposes, on one hand, measuring the impact of the morbidity-mortality avoided by the drug on the use of the healthcare services and, on the other hand, estimating at what point the levels of efficacy and risk in actual practice depend on specific organisational conditions or the existence of special competencies in the healthcare system.
- *'Joined' population*: This describes the population that actually benefits from the drug in 'real life'. The constitution of this population depends particularly on the place of the drug in the therapeutic strategy and the modalities of identifying the target population in everyday prescribing practice.
- *Utilisation review*: This describes the actual conditions of use of the drug. These depend particularly on physician prescribing practices and the patient compliance.

Concerning the analysis of the current system and in order to structure the debates during the workshop, a questionnaire was prepared for all the participants (table I).

3. Questions and Methods

The questions posed by the evaluation of the benefit of a drug to public health highlight several distinct categories: efficacy in actual situations; safety in actual situations; prognostic factors and patients who respond; place in the therapeutic strategy; impact on the healthcare system; the 'joined' population; and utilisation review. The experimental approach cannot alone respond to all these questions. Without challenging the pertinence of this approach in producing information about the drug, this established fact has the merit of clearly distinguishing between

two phases in the life of a drug: on the one hand, the clinical development up to the AMM, where the experimental approach is essential; and, on the other, the postmarketing studies, where the place of the different categories of approach (experimental, observational or modelling) according to the type of question raised by the population analysis requires a case-by-case consideration.

Recent studies have employed a certain number of examples to evaluate the level of proof of the observational approaches with respect to the experimental approaches.^[2-6] Overall, these studies underline the complementary nature of the two approaches as far as health evaluation is concerned.

The inventory of the methods of pharmacoepidemiology, a discipline in which the precise aim is to propose methods for studying the impact of a drug in actual situations of use, would be a writing project, which is not the objective of a round table.

A previous round table^[7] was specifically devoted to the quality criteria of pharmacoepidemiological studies.

There, the debates allowed the qualification of each category of approach with regard to the categories of question identified. The strengths and the limits of different approaches when they are applied to answer different questions have been described. Thus, the round table was able to agree on the formulation of a table (table II).

4. The Current System for ISP Study Projects

The participants analysed the current system in the light of the responses to the questionnaire distributed earlier. Proposals have been made aimed at optimising this system. This part of the round-table debate has not been included in the present article at the request of the sponsorship committee of the Giens meetings, because it would depart from the objectives of these meetings.

Table I. A previous questionnaire about the current system

A. Postmarketing studies: state of play

- A1. Who draws up the questions and at what stage in the process?
- A2. Who sets the objectives?
- A3. What types of studies?
- A4. Who sets the methods/evaluates them/choice of service providers?
- A5. Who finances it?
- A6. How is scientific independence guaranteed – protocol and follow-up?
- A7. Who carries out their evaluation?
- A8. What are the aims of the different participants?

B. Overview of the studies of the public health benefit of drugs: the institutional players

- B1. Where would you site the possible interventions by the industry?
- B2. The positive points?
- B3. The sticking points?

C. Proposals for improvement

Table II. Categories of postmarketing questions and methodological approaches

	Methodological approaches		
	experimental	observational	modelling
Efficacy in actual situations; benefit to the population	Pragmatic studies; clinical mega-trials; intervention studies – randomisation by clusters; benefit of meta-analyses	Suitable comparative studies (case-control and cohort) to confirm efficacy in actual situations, also shown in clinical trials; attention to indication bias; <i>special cases</i> : sometimes the observational approach is the only one feasible for the evaluation of efficacy in actual situations; benefit of meta-analyses	Modelling, starting with substitution criteria; vaccination models
Safety in actual situations	Pragmatic studies have better reliability compared with explanatory studies; clinical mega-trials; benefit of meta-analyses	Databases that can be used; notification of AEs (surveillance) provides qualitative information; comparative case-control and cohort studies; benefit of meta-analyses	Standardisations can be used on the basis of data from explanatory trials
Prognostic factors; patients responding and at-risk patients	Pragmatic studies can contribute to the identification of prognostic factors; benefit of meta-analyses	The observational approach, combined with suitable statistical analyses, is the reference tool for the investigation of prognostic factors	
Place in the therapeutic strategy	Pragmatic studies; clinical mega-trials; intervention studies – randomisation by clusters; benefit of meta-analyses	Descriptive studies allow the analysis of concordance between the strategy envisaged and that in everyday life; comparative studies can be used to evaluate therapeutic strategies	
Impact on the healthcare system	Pragmatic studies can be adapted	Descriptive observational studies to document the conditions of management; comparative observational studies to evaluate the impact on the healthcare system	Modelling is a tool suited to the evaluation of impact on the healthcare system; the extrapolation from data from other studies is sometimes the only possible approach
'Joined' population (those who actually obtain benefit); capacity to identify; target pop./'joined' pop.	Diagnostic trials suited to the evaluation of the ability to identify the target population; experimental approaches are not suited to the identification of target and 'joined' populations	Databases can be used; representativity; bias involving changes in practice; discussion and analysis of the biases	Can be adapted to quantification of the target population
Drug utilisation review; prescribing conditions; use by the patient	Unsuitable methods	Databases can be used; representativity; bias involving changes in practice; <i>usage studies</i> : which criterion? who defines it?; discussion and analysis of the biases	

AE = adverse effects.

5. The Databases

During the round table, attention was drawn to the existence of several databases, and the benefits they offer in the context of initiating postmarketing studies were emphasised. Of course, this concerns databases such as that of the 'Assurance Maladie' (sickness insurance) and especially the SNIIR-AM (Système National d'Informations Inter-Régimes de l'Assurance Maladie [national system of inter-organisation sickness insurance information]).

SNIIR consists of a 'store' of all the data of the 'Assurance Maladie'. It involves data provided by the reimbursement systems of all the organisations. The data relate to individual patients; they are anonymous as far as the beneficiaries and individ-

uals are concerned, but are open to examination by health professionals and health organisations.

Entries in the SNIIR-AM for the general organisations began in January 2002. During 2003, all the organisations will supply data from 2002, considered as the test year. The first two 'outlets' or DATAMART (dépenses de santé et offre de soins [health expenditure and care provision]) should be available during the second semester of 2003. The records will be stored for a period of 3 years.

Apart from the 'Assurance Maladie' database, there are also databases of epidemiological records on the INSERM site and other public databases such as those of INSEE or CREDES etc.

Finally, there are private databases such as IMS, Thalès and GERS.

The participants emphasised the importance of obtaining a very detailed assessment of information that could help in using those databases before initiating *ad hoc* studies.

Participants

M.N. Banzet (Servier, Neuilly-sur-Seine), C. Blachier (Novartis, Rueil-Malmaison), P. Blin (ICARE, Massy-Palaiseau), M. Bouhassira (Lilly France, Saint-Cloud), G. Bouvenot (CHU, Marseille), G. Bréart (INSERM, Paris), J.P. Daurès (IURC, Montpellier), F. de Cremiers (Wyeth Lédérle, Paris), C. Duguay (Sanofi-Synthelabo, Le Plessis-Robinson), E. Eschwege (INSERM U21, Villejuif), F. Fagnani (CEMKA, Bourg-la-Reine), A. Fontbonne-Bayner (INSERM U500, Montpellier), I. Giri (LIR, Paris), J.M. Hotton (Pfizer, Paris), F. Ichou (Aventis, Paris), P. Jolliet (CHU, Nantes), J.M. Joubert (Produits Roche, Neuilly), R. Koen (Pharmacia SAS, Saint-Quentin en Yvelines), D. Lagarde (Ministère, Direction des Hôpitaux), C. Le Jeunne (HEGP, Paris), E. Leutenegger (ABR PHARMA, Paris), T. Marquet (Lunbeck, Paris), J. Massol (CHU, Besançon), F. Meyer (Afssaps, Saint-Denis), J. Micallef (CPCET, Marseille), S. Paulmier-Bigot (LEEM, Paris), P.F. Ploin (HEGP, Paris), Y. Ract (CNAMTS, Paris), A. Rauss (Afssaps, Saint-Denis), M. Ricatte (CNAMTS, Paris), H. Sainte-Marie (Ministère de la Santé, DGS, Paris), S. Tardieu (DRI, Marseille), D. Vesque (Pharmacia et Upjohn, Saint-Quentin en

Yvelines), J.M. Vetel (CHR, Le Mans), M. Vray (Institut Pasteur, Paris), P. Watteau (Bayer, Puteaux).

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Correspondence and offprints: *Catherine Le Galès*, INSERM U537, Hôpital Kremlin-Bicêtre, 80 rue du Général Leclerc, 94276 Le Kremlin-Bicêtre, France.

E-mail: U537@kb.inserm.fr