Agenzia Italiana del Farmaco

AIFA

Independent research on drugs **funded by the Italian Medicines Agency**

BACKGROUND

The promotion of independent research on drugs represents one of the strategic tasks assigned to the Italian Medicines Agency (AIFA) by legislation. The general aim of the program is to support clinical research on drugs in areas of interest for the National Health Service (NHS) and where commercial support is normally insufficient.

There is not only a concern for patient populations normally excluded by clinical studies on efficacy and safety, such as children, pregnant women and the elderly. There is also a need to obtain more information on research issues less explored in commercial research, such as clinically relevant end points, relative efficacy of drugs (including the assessment of multimodal strategies), and long term follow up on efficacy and safety of therapies.

AIFA set up the program on independent research in 2005, and two call for proposals (2005 and 2006) have already been launched. The call for proposals is aimed at investigators working in public (e.g., NHS, universities, etc.) or non-profit organisations (e.g., scientific foundations, patient associations, etc.). For the first two years, three main areas of drug research were included in the program:

Area 1. Orphan drugs for the treatment of rare diseases and drugs for non-responders.

Area 2. Head to head comparison of drugs and therapeutic strategies.

Area 3. Strategies to improve the appropriateness of drug use and pharmacoepidemiology studies.

Lack of support in the area of rare diseases generally stems from the limited segment of patient populations involved. Comparative studies, especially when generics are included, and strategies aimed at providing effective and independent information to GPs and patients, also suffer from a considerable degree of neglect.

ABOVE: Luca Bertinotti, *Old Pubmed*

BELOW: Gabriella Sartini, *Il pezzo mancante (The missing piece)*

THE AIFA FUND

An innovative aspect of the program is represented by the way of funding independent research: an *ad hoc* fund was set up, requiring pharmaceutical companies to contribute 5% of their yearly expenditure devoted to promotional initiatives (e.g., seminars, workshops, etc.) aimed at physicians. Around 40 million Euro is available each year for funding the research program and the other activities supported by this fund: independent drug information and the reimbursement of orphan drugs, and “life saving” drugs, not yet marketed.

With the help of an independent scientific committee (Committee for Research and Development, R&D), specific research areas are identified. The role of the R&D Committee is to support AIFA in identifying research areas for the call for proposals, conducting the first phase of the selection process, and supervising the implementation of the projects.

THE EXPERIENCE FROM 2005 TO DATE

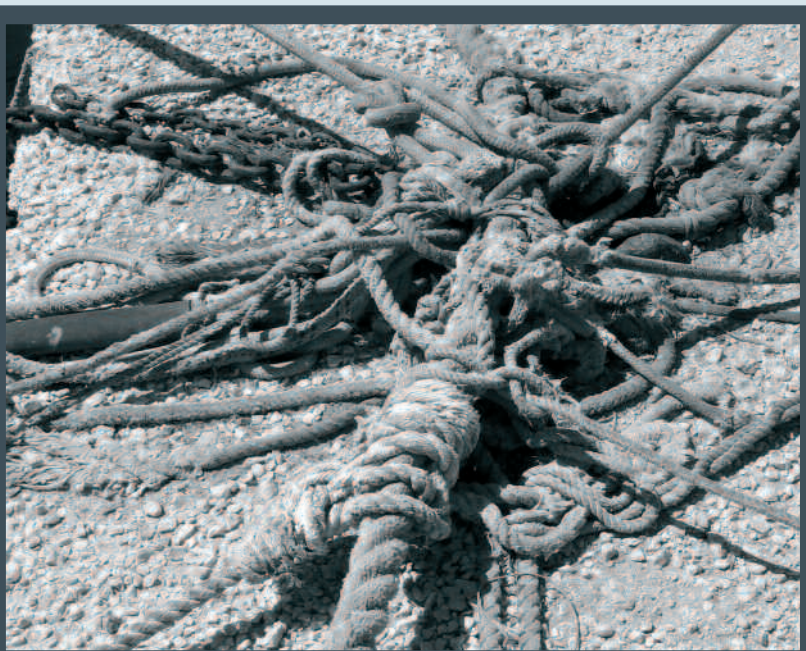
For the 2005 call for proposals, out of the 402 letters of intent originally submitted, 101 were admitted to the second phase of the evaluation (study sessions), and 54 studies were funded (Table 1). All funded studies are currently underway.

Table 1. Study projects of the Italian program for independent research on drugs, per research area

	Call for proposals 2005			Call for proposals 2006		
	Letters of intent	Study protocols	Funded protocols	Letters of intent	Study protocols	Funded protocols
Area 1: Orphan drugs	150	31	20	184	38	24
Area 2: Head to head comparison of drugs	80	25	13	121	24	16
Area 3: Pharmacovigilance and appropriateness	172	45	21	149	37	11
Total	402	101	54	454	99	51

The 2006 call for proposals has now been concluded (a synthesis of the content is presented in Appendix 1). Out of 454 letters of intent, 99 were admitted to the study sessions and 51 were funded.

The R&D Committee is currently defining the research topics to be included in the next call for proposals, due in August 2007. Hearings with different scientific and health institutions have taken place and an ad hoc web site was opened to receive suggestions from individual researchers, learned societies, patient associations, research groups, etc.



Chiara Florio, *Basta saper guardare (You only need to know how to look)*

Appendix 1. The 2006 AIFA program for independent research on drugs: study topics by areas and general information on the call for proposals

Area 1. Orphan drugs for the treatment of rare diseases and drugs for non-responders

Topic	Description
1	Assessment of the benefit-risk profile of orphan drugs, approved or designated by the EMEA, for the treatment of rare diseases. *NB: to check whether a drug is included in the EMEA list please consult the web site http://ec.europa.eu/enterprise/pharmaceuticals/register/alforphreg.htm*
2	Assessment of the benefit-risk profile of off-label drug use for the treatment of rare diseases. *NB: only rare diseases listed within the web site of either the Istituto Superiore di Sanità (ISS) (www.iss.it) or the National Institutes of Health (NIH) (http://rarediseases.info.nih.gov) will be considered.*
3	Assessment of the benefit-risk profile of drugs for non-responders to standard treatments. *NB: this research topic is aimed at subgroups of patients who do not respond to standard therapies (e.g., because of the genetic modification of drug metabolism or targeting), and for whom a rationale for substitute treatments is available. The studies need to be aimed at the patient population whose prevalence is equivalent to that of rare diseases and for which commercial research is lacking. Cancer treatments are excluded.*

Roberto Bruno, *Se non pensiamo alla Ricerca il tutto non ha senso (There is no meaning without research)*

Area 2. Comparisons among drugs and among therapeutic strategies for the treatment of clinical conditions of relevant interest for the public health and the NHS

Topic	Description
1	Therapeutic strategies for optimising the treatment of stroke. *NB: this research topic is aimed at studying the efficacy of thrombolytic drugs in association with other drugs, and/or within therapeutic strategies, with specific attention to the dose, timing, and administration of drugs.*
2	Therapeutic strategies including the comparison among oral hypoglycemics for the treatment of type II diabetes.
3	Therapeutic strategies for the treatment of patients concomitantly affected by COPD (Chronic Obstructive Pulmonary Disease) and heart failure.
4	Therapeutic strategies for the treatment of asthma. *NB: this research topic is particularly aimed at studying the benefit-risk profile of long-acting beta$_2$-adrenergics and of anti-IgE monoclonal antibody.*
5	Therapeutic strategies for optimising the treatment of new anticancer targeted drugs. *NB: this research topic is aimed at optimising the duration of therapy, dosage, and concomitant use, of targeted drugs (e.g., monoclonal antibodies, tyrosine kinase inhibitors).*
6	Therapeutic strategies for optimising the use of general anaesthetics and muscle relaxant in surgery. *NB: this research topic is aimed at comparing the benefit-risk profile of different anaesthetic options in surgery.*
7	Therapeutic strategies for patients requiring dialytic treatments. *NB: this research topic is aimed at comparing the benefit-risk profile of therapies for the prevention of complications (e.g., anaemia, hyperlipaemia, etc.) in patients requiring dialytic treatments.*
8	Therapeutic strategies for the prevention of osteoporotic fractures. *NB: this research topic is aimed at conducting "head to head" comparisons between drugs, and at assessing pharmacological and non-pharmacological therapeutic strategies (e.g., information and education in relation to diet, physical exercise, strategies to reduce the risk of fractures).*
9	Therapeutic strategies for the treatment of pain in paediatrics. *NB: this research topic is aimed at assessing the benefit-risk profile of drugs in the treatment of pain (with particular attention to post-surgical and post-traumatic pain, and of pain arising during invasive procedures).*
10	Therapeutic strategies for optimising the use of cardiovascular drugs in paediatrics and neonatology.

Area 3. Pharmacoepidemiological studies aimed at defining the benefit-risk profile of treatments and the impact of strategies for improving the appropriateness of drug use

Topic	Description
1	Studies on the benefit-risk profile of psychopharmacological treatments for children and adolescents.
2	Studies on the benefit-risk profile of antipsychotic drugs in the treatment of patients with dementia. *NB: this research topic is aimed at assessing therapeutic strategies that include the comparison between second and third generation antipsychotics.*
3	Studies on the benefit-risk profile of drug use in pregnancy and of fertility treatments. *NB: this research topic is aimed at studying the maternal and foetal adverse events, at optimising the treatment of diabetes during pregnancy and of hormones used in assisted reproduction.*
4	Assessment of the benefit-risk profile of bisphosphonates use. *NB: this research topic is primarily concerned at quantifying the severe adverse events associated with the use of bisphosphonates (e.g., osteonecrosis of the jaw).*
5	Studies on the prophylaxis and therapy of viral hepatitis B. *NB: this research topic is aimed, on one hand, at comparing the benefit-risk profile of antiviral drug treatments, and on the other hand at assessing immunity against hepatitis B in children who received vaccines with low immunogenicity.*
6	Studies on pharmacological treatments of chronic headache. *NB: this research topic is also aimed at studying the occurrence of addiction and headaches attributed to the excessive use of NSAIDs and triptans.*
7	Studies on the use of albumin and immunoglobulins in clinical practice.
8	Studies on the use of combined treatments in elderly patients with multiple diseases. *NB: this research topic is aimed at studying patients affected by hypertension, diabetes, cardiovascular diseases, also in association with other clinical conditions. The application to these patients of available guidelines, and the quantification of adverse events attributable to drug interaction is also assessed.*
9	Studies for assessing the impact of independent information addressed to the public, and/or patient associations, on the appropriateness of drug use and on pharmaceutical expenditure. *NB: this research topic is aimed at assessing, through a randomised or observational design conducted at least on a regional scale, the impact of educational and organisational interventions.*

Hundreds of images were submitted in 2006 for AIFA's second annual photo contest with the theme "Research". Italian physicians and pharmacists were invited to participate. The Agency selected the winners (some of them shown here) on the basis of originality and execution. To view more contest submissions and learn how to enter 2007 competition, click on www.agenziafarmaco.it

AIFA

The Italian Medicines Agency (AIFA) is a governmental institution operating within the Ministry of Health in collaboration with Regional Health Authorities. AIFA aims at protecting public health through the continuous assessment of the risk-benefit profiles of medicinal products, the support of innovation and the promotion of appropriate drug use.

AIFA activities include, among the others, marketing authorisation of medicinal products, pharmacovigilance, monitoring of clinical trials, inspections of products and manufacturing process, independent information, promotion of research, drug expenditure governance.

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THE SELECTION PROCESS

The evaluation procedure mirrors the accredited standards of internationally recognised scientific institutions.
The assessment of projects is based on the following criteria:

- Relevance of the expected results for the clinical practice within the NHS;
- Scientific validity, in order to select projects with the highest scientific merit;
- Potential impact on the regulatory activity of AIFA, with specific attention to guide the decision about drug reimbursability and limitations of use within the NHS;
- Lack of commercial interest for the objectives of the study, in order to use available resources on important though neglected areas of interest.

A two step review process has been implemented. In the first step, researchers are required to submit a “letter of intent” (i.e. a synthesis of the study protocol) which is assessed by the R&D Committee. Investigators admitted to the second phase of the evaluation are required to present a full study protocol.

The evaluation of the study protocols entailed the organisation of independent study sessions, involving more than 20 experts (half from Italian institutions and half from abroad).
In order to guarantee independence in the evaluation procedure, no R&D Committee members were included in the study sessions (see Box 2). Two written comments were obtained for each study protocol before the study session meeting. Each protocol was also thoroughly reviewed in a plenary discussion, and a final score, representing the average of each expert’s vote, was achieved. Study protocols were ranked on the basis of the final score and, starting with the highest score, the available funds (35 million Euro in 2005 and 31 in 2006) were distributed accordingly.

Mario Baruchello, *Il medico della persona e la ricerca della relazione empatica: dall'high tech all'high touch (From high tech to high touch)*

Members of AIFA Research & Development Committee

Lucio Annunziato; Renato Bernardini; Sergio Bonini; Maria Del Zompo; Antonio Francavilla; Enrico Garaci; Silvio Garattini (chairperson); Alessandro Liberati; Giampietro Rupolo; Gloria Saccani Jotti.

Members of the Study Sessions 2006

Ségoléne Ayme (INSERM SC11, Paris, France); Marco Bobbio (Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy); Jean-Pierre Boissel (Service de Pharmacologie Clinique Faculté RTH Laennec, Lyon, France); Xavier Bonfill (Iberoamerican Cochrane Centre, Hospital de Sant Pau, Universitat Autonoma de Barcelona Sant Antoni, Spain); Jean Bousquet (Université de Montpellier, France); Paola Facchin (Università di Padova, Padova, Italy); Graziella Filippini (Istituto Neurologico Besta, Milano, Italy); Claudio Fiocchi (The Cleveland Clinic Foundation, Lerner Research Institute, Cleveland, USA); Robert Goldstein (Juvenile Diabetes Research Foundation, New York, USA); Catherine Hill (Gustave Roussy Institute, Villejuif, France); A Pali S Hungin (Centre for Integrated Health Care Research, The Wolfson Research Institute, University of Durham, UK); Xavier Kurz (European Medicines Agency (EMEA), London, UK); Bruno Lunenfeld (Bar-Ilan University, Ramat Gan, Israel); Nicola Magrini (Centro per la Valutazione dell'Efficienza dell'Assistenza Sanitaria, Modena, Italy); Giovanni Migliaccio (Istituto Superiore di Sanità, Roma, Italy); Marcello Orzalesi (Ospedale Pediatrico Bambino Gesù, Roma, Italy); Luigi Pagliaro (Ospedale V. Cervello, Palermo, Italy); Gregory Pastores (New York University, New York, USA); Lorenzo Pavone (Universita di Catania, Italy); Paolo Preziosi (Università Cattolica Sacro Cuore, Roma, Italy); Anita Regalia (Ospedale S. Gerardo, Monza, Italy); Paolo Maria Rossini (Campus Biomedico, Roma, Italy); Holger Schunemann (Istituti Fisioterapici Ospitalieri Regina Elena, Roma, Italy).

GENERAL RULES FOR THE 2006 CALL FOR PROPOSALS

When submitting a letter of intent to the 2006 AIFA program on independent research on drugs, the following information was taken into account:

- Each proponent might present, as principal investigator, only one letter of intent.
- Principal investigators of projects funded in the 2005 could not apply (as principal investigators) for the 2006 call for proposals.
- Letters of intent were not accepted if the content was considered equivalent, by the R&D Committee, to a project funded in the 2005 program (to consult the titles: www.agenziafarmaco.it).
- Clinical units where patients were planned to be enrolled could not be involved in more than 3 letters of intent pertaining to the research areas 2 and 3.
- If a multinational study was proposed, it should have been considered that the funding from AIFA was limited to the Italian portion.
- This call focused on clinical research and consequently letters of intent focusing on the drugs mechanism of action were not accepted.
- Phase I and phase II clinical studies were not considered acceptable, with the exception of adequately motivated studies concerning orphan drugs designated by the EMEA.
- AIFA funded projects in area 1 up to a maximum of 300,000 Euro for each proposals (the cost of therapies was funded separately).
- Letters of intent were submitted by 30 September 2006, through the AIFA website (www.agenziafarmaco.it).

ABOVE: Raffaele Garribba, *Ricerca è... sciogliere nodi (Research means disentangling knots)*
BELOW: Filippo Romaniello, *Mira (Aim)*

Public and private companies that were interested in providing financial support to the 2006 AIFA program for independent research had to comply with the following criteria:

Pharmaceutical companies might provide drugs that were under investigation in projects in area 1.

Pharmaceutical companies might provide drugs that were reimbursed within the NHS if a double blind preparation was needed.

Pharmaceutical companies might provide financial contribution to projects in area 1, topic 1.

For all other topics (topics 2 and 3 in area 1; all topics in area 2 and area 3) public and private companies might provide financial support to an entire area or topic, and not to a specific project, taking into account that funding did not exceed 500,000 Euro and that the willingness to contribute was communicated before the assessment of the letters of intent had been completed (or by 30 November 2006).