Agenzia Italiana del Farmaco

AIFA

Independent research on drugs funded by the Italian Medicines Agency

The promotion of independent research on drugs represents one of the strategic tasks assigned to the Italian Medicines Agency (AIFA) by the legislation. An interesting and innovative aspect is represented by the way of funding independent research: an ad hoc fund was set up, requiring pharmaceutical companies to release 5% of their expenditure devoted to promotional initiatives aimed at physicians.

AIFA set up the program on the independent research in 2005; two call for proposals (2005 and 2006) have already been launched, and overall 105 projects have already been funded. The objective of the present document is to provide guidelines for the 2007 call for proposals.

The general aim of the program is to support clinical research on drugs in areas of interest for the National Health System (NHS) and where commercial support is normally insufficient. This situation represents a specific concern in case of:

- Rare diseases;
- Patients normally excluded by clinical studies on efficacy and safety, such as children, pregnant women and the elderly;
- Large populations with important implications for public health and for the NHS economic affordability;
- Comparative studies, especially when generics are included, and strategies aimed at providing effective and independent information to GPs and patients.

With the help of an independent scientific committee (Committee for Research and Development, CRD), chaired by prof. Silvio Garattini, three areas of research were identified for the 2007 program:

1. Orphan drugs for the treatment of rare diseases and drugs for non-responders;
2. Comparisons among drugs and among therapeutic strategies for the treatment of clinical conditions of relevant interest to public health and the NHS;
3. Pharmacoepidemiological studies aimed at defining the benefit-risk profile of treatments and the impact of strategies for improving appropriate drug use.

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

Four topics are included in this area. The first one relates to orphan drugs that are approved or "designated" by the EMEA. The second one concerns drugs that are used off-label for the treatment of rare diseases. The third one is relevant to sub-group populations of non-responders to standard treatments, for which pharmaceutical companies lack interest in finding new evidence for "niche" indications. The last topic focuses on drugs for the treatment of the multi-resistant tuberculosis and other tropical diseases in Italy. Even taking into account the limited magnitude of the populations involved, studies should normally follow a comparative design.

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

Nine topics are included in this area. Only phase III and phase IV randomised studies will be considered. Studies need to include drugs reimbursed by the NHS and compare the benefit-risk profile of different drugs (including generics). Studies may also include comparisons between

pharmacological and non-pharmacological interventions. Priority will be given to fragile patients (e.g., children and the elderly) and, whenever compatible with the study rationale, to low cost and generic drugs.

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

This area, which includes nine topics, mainly concerns largely used marketed drugs whose benefit-risk profile needs to be re-evaluated. Differently from area 2, study design may have, on the basis of the specific question, either an experimental or observational design. Particular attention will be given to fragile patients (e.g., children and the elderly) especially when multiple treatments are concomitantly administered. Studies aimed at assessing the impact of strategies for the promotion of the appropriateness of drug use are also included. The study design of these projects should include process indicators and whenever possible, clinical or subjective endpoints; the assessment may be based on concurrent control groups and/or on "before-after" comparisons.

Research topics by areas

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

Area 1		
Area	Topic	Description
1	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.
1	2	Assessment of the benefit-risk profile of off-label drug use for the treatment of rare diseases. NB: only rare diseases listed in 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/asp/diseases/diseases.asp) will be considered.
1	3	Controlled clinical trials aimed at assessing the efficacy of pharmacological treatments in patient populations previously identified, on a phenotypic and/or genotypic bases, as non-responders to standard treatments. NB: this research topic is aimed at subgroups of patients already identified as refractory to standard therapies, and for whom it is already known a genotypic or phenotypic characteristic which enables the identification of a subgroup within the entire patient population.
1	4	Controlled clinical trials aimed at assessing the benefit/risk profile of drugs for the treatment of multi-resistant tuberculosis and tropical and sub-tropical diseases in Italy (Leishmaniasis, filariasis, malaria, trypanosomiasis, etc.). NB: this research topic refers to comparative studies aimed at evaluating the benefit-risk profile of different therapeutic strategies, especially studies testing drug combinations, and also assessing the long term efficacy of such treatments.

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

Area 2		
Area	Topic	Description
2	1	Comparisons among drugs or among therapeutic strategies in children: optimization of the use of cardiovascular drugs, antidiabetics, and antiasthmatics. NB: only comparative studies including also non pharmacological therapies are admitted in the field of the antiasthmatic drugs.
2	2	Therapeutic strategies for optimising the use of anaesthetics and muscle relaxant in surgery. NB: this research topic particularly refers to comparative studies aimed at evaluating the benefit-risk profile of different anaesthetic and myoresolutive strategies for specific surgery interventions.
2	3	Comparisons among drugs and among therapeutic strategies (including non pharmacological strategies) for the prevention of osteoporotic fractures. NB: this research topic is aimed at conducting "head to head" comparisons between specific treatments within therapeutic strategies and concers both pharmacological or non-pharmacological therapeutic strategies (e.g., information and education interventions in relation to diet, physical exercise, strategies to reduce the risk of fractures).
2	4	Controlled trials comparing pharmacological strategies for the treatment of myocardial infarction and heart failure in women.
2	5	Comparisons among drugs and among therapeutic strategies for the treatment of inflammatory autoimmune diseases.
2	6	Comparisons among therapeutic strategies for the optimization of pain therapy in neoplastic patients. NB: this research topic refers to the following comparative studies: A) comparisons among drugs; B) comparisons between drugs and non pharmacological therapeutic strategies; C) comparisons between drugs and combinations of drugs and non pharmacological strategies.
2	7	Comparisons among therapeutic strategies used in intensive care, especially focussing at the prevention and treatment of respiratory infections and sepsis. NB: In the case of antibacterial drugs, impact of the treatment on the development of drug resistance should be evaluated.
2	8	Comparisons between different gastro-protective treatments in elderly patients. NB: this research topic refers to the following patient populations: A) patients with reflux disease; B) patients who undergo short treatment with NSAIDs (including COXIBs); C) patients who undergo treatment with glucocorticoids.
2	9	Comparisons between therapeutic strategies for the optimisation of therapy for Parkinson's disease.

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.

Area 3		
Area	Topic	Description
3	1	Assessment of the benefit-risk profile of pharmacological treatments in pregnant women. NB: this research topic refers to studies aimed at assessing the benefit-risk profile of pharmacological treatments in pregnant women and during the peri-natal period.
3	2	Studies on the long term benefit-risk profile of drugs used in the treatment of HIV. NB: this research topic refers to studies that have been ongoing for at least 3 years now and are lacking of adequate economic funds to continue follow-up of patients already enrolled.
3	3	Assessment of the benefit-risk profile of psychotropic drugs also used in combination with psychotherapies. NB: this research topic concerns two main aspects. The first one is relevant to the comparative assessment of the impact of the pharmacological treatment (used as monotherapy or in combination) also combined with psychotherapies in the treatment of anxiety and depressive disorders. The second aspect concerns the potential usefulness of specific psychotherapeutic treatments as supportive interventions to ameliorate the compliance to pharmacological therapies in the treatment of serious mental disorders (schizophrenia and bipolar disorder).
3	4	Studies for assessing the impact of independent information addressed to patients and/or patient associations, on the appropriateness of drug use and/or the risks related to drug interactions NB: this research topic refers to randomised or observational studies aimed at assessing the impact on the appropriateness of drug use and/or the reduction of the risks related to drug interactions.
3	5	Studies on the efficacy of distance learning interventions to determine modifications in the appropriateness of drug prescribing. NB: this research topic refers to randomised or observational studies aimed at assessing the impact on the appropriateness of drug use and/or the reduction of risks related to drug use.
3	6	Assessment of the risk-benefit profile of therapeutic strategies involving pharmacological and non pharmacological treatments, in the therapy of drug addiction. NB: this research topic refers to addicted subjects whose addiction is principally due to opioids or psychostimulants.
3	7	Outcome assessment of treatments with drugs within the therapeutic group of inhaled anticholinergics and inhaled corticosteroids.
3	8	Systematic review of therapeutic questions on pharmacological topics characterized by great uncertainty and for which no systematic reviews are available in scientific literature. NB: these studies should be concluded within 12 months from the approval date.
3	9	Assessment of long term benefit-risk profile of pharmacological treatments for patients affected by hypothyroidism.

General information on the 2007 call for proposals

The following information is to be taken into account when submitting a letter of intent to the 2007 AIFA program on independent research on drugs:

- Each proponent may present, as principal investigator, only one letter of intent.
- Principal investigators of projects funded in 2005 and 2006 cannot apply (as principal investigators) for the 2007 call for proposals.
- Letters of intent will not be accepted if the content is considered equivalent, by the Committee for Research & Development (CRD), to a project funded in the 2005 and 2006 programs (titles can be consulted at: www.agenziafarmaco.it).
- Clinical units where patients are planned to be enrolled may not be involved in more than 3 letters of intent pertaining to the research areas 2 and 3.
- If a multinational study is proposed, please consider that the funding from AIFA is limited to the Italian portion.
- This call focuses on clinical research and consequently letters of intent focusing on drug mechanisms of action will not be accepted.
- Phase I and phase II clinical studies will not be accepted, with the exception of adequately motivated studies concerning orphan drugs designated by the EMEA.
- AIFA will fund projects in area 1 up to a maximum of 300,000 euros for each proposals (the cost of therapies will be funded separately).
- Letters of intent will have to be submitted by 1st October 2007, through AIFA website (www.agenziafarmaco.it).

Public and private companies that are interested in providing financial support to the 2007 AIFA program for independent research will have to comply with the following criteria:

- Pharmaceutical companies may provide drugs that are under investigation in projects in area 1.
- Pharmaceutical companies may provide drugs that are reimbursed within the NHS if a double blind preparation is needed.
- Pharmaceutical companies may provide financial contribution to projects in area 1.1.
- For all other topics (topics in area 1.2, 1.3 and 1.4; area 2 and area 3) public and private companies may provide financial support to an entire area or topic, and not to a specific project, taking into account that funding does not exceed 500,000 euros and that the willingness to contribute has to be communicated before the assessment of the letters of intent has been completed (or by 30 November 2007).
- When communicating the results of the selection process all public and private supports will be made public.

Transparency and independence of the selection procedures

The assessment of projects will be based on the following criteria:

- Scientific validity in order to select projects with the highest scientific merit;
- Relevance of the expected results for the clinical practice within the NHS;
- Potential impact on the regulatory activity of AIFA, with specific attention on 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.

The evaluation procedure is based on a two step process. The first step concerns the letters of intent and is carried out by the CRD. For letters of intent admitted to the second step, principal investigators are required to provide a study protocol, which will be evaluated by independent commissions (study session) including experts from Italy and abroad. Study protocols will be ranked on the basis of a final score and, starting with the highest score, the available funds will be distributed accordingly.

Transparency will be guaranteed during the entire selection process and the criteria adopted to make decisions will be made public. Moreover, expert names and conflict of interest declarations will be publicised (Table 1).

Evaluation procedures

In the first evaluation phase (triage), carried out by the CRD, each letter of intent is preliminary reviewed by at least three members of the CRD. The following plenary discussion selects the projects that will be admitted to the second phase. In assigning the score the following criteria are followed:

- scientific merit of the study: up to 35 points
- relevance for the NHS: up to 35 points
- scientific qualification and experience of the proponents and of the participating unit: up to 20 points
- budget adequacy: up to 10 points

Table 1. Procedures for the call for proposals publication, submission and evaluation of studies

Subjects involved	**Deadline**
AIFA announces calls for proposals (one for each area of interest) and gives details about the requirements and procedures that are adopted for the submission and assessment of projects	1 August 2007
Participants who intend to take part will submit a "**letter of intent"** (in Italian) to AIFA	1 October 2007
CRD evaluates the letters of intent (triage) and selects studies which will be admitted to the second evaluation phase	30 November 2007
Selected participants are asked to submit a **study protocol** (in English) to AIFA	21 January 2008
Study protocols are evaluated by independent experts (from Italian and international institutions) during "study sessions".	31 March – 2 April 2008
The assessment made by the study sessions will be ratified by the CRD and will be submitted to the Management Board for final approval	April 2008
A formal agreement regulating the relationship between AIFA and principal investigators will be signed	May 2008

CRD: Committee for the Research & Development.