AIFA – Italian Medicines Agency

Working Group on Innovative Drugs

CRITERIA FOR RANKING THERAPEUTIC INNOVATION OF NEW DRUGS

and elements for supplementing the dossier for admission to the reimbursement system

(document approved by the CTS on July 10, 2007)

Introduction

Innovation in drug therapy is a source of continuing debate[1,2,3] for all those who, for various reasons, are concerned with drugs: manufacturers, regulatory agencies, academia, health care professionals and patients. The term "innovative" often tends to be used to define a *new* drug proposed for entry onto the market, while it is instead necessary to find a more precise definition of this term.

A first definition of what could be meant by *therapeutic innovation* emerged from a meeting held by the *International Society of Drug Bulletins* (ISDB) in 2001[4] in which, amongst other things, it was established that the term innovation can have various meanings.

Therapeutic innovation represents an important objective for public health and its definition can constitute a means that can be used by AIFA, in order to assign the reimbursement class and for price negotiation, to classify drugs about to enter onto the market in Italy, giving more value to those that represent a *therapeutic innovation*.

Model for ranking the therapeutic innovation of a new drug

The starting model proposed by the working group was derived from a recent publication[5] by some of the working group members. After evaluating this model, and taking into account the suggestions that emerged during the working group meetings, it was decided to offer the method to the Farmindustria experts who raised some objections that were partially accepted in this new version of the document.

Preliminary division of drugs on the basis of the therapeutic target

The preliminary division of new drugs (or of new therapeutic indications for drugs already on the market) potentially classifiable for the purposes of therapeutic innovation takes into account the

nature of the target disease (the therapeutic target). *Certainly, the social as well as the therapeutic impact of drug intended for the treatment of a serious disease is in itself greater than the impact of a molecule designed for the treatment of non-serious diseases.* Three classes, in decreasing order of importance have therefore been defined:

1. (**A**) drugs for the treatment of serious diseases, defining serious as a disease that causes death or hospitalisation, is life-threatening or can lead to permanent inability (e.g. cancer, Parkinson's disease, AIDS, etc.);
2. (**B**) drugs for the treatment of risk factors for serious diseases (e.g. hypertension, obesity and osteoporosis);
3. (**C**) drugs for the treatment of non-serious diseases (e.g. allergic rhinitis).

It should be stressed that proposing a drug for a serious disease is not in itself sufficient to define the degree of innovation: it is above all important that this new drug produces a substantial benefit for this disease. On the other hand, a drug for a non-serious disease, if it addresses a disease for which there is no treatment, and guarantees a good level of effectiveness, should be considered a therapeutic innovation to all effects and purposes. The EMEA has also established the severity of the target disease as an essential parameter for deciding which drugs must have an accelerated assessment procedure (http://www.emea.cu.int/pdfs/humanlregaffair/049596en.pdf).

In short, the target disease must be classified first in order to achieve a dual aim:

- prioritise drugs that are designed for diseases with a significant clinical and social impact.
- without, however, neglecting drugs that, while designed for minor disease, still represent a true therapeutic innovation.

These elements represent the basic criteria for admission of new drugs to the reimbursement system. In addition, the prevalence in the population of the target disease must also be considered, since an innovative drug for a rare disease has a very different economic impact on the community with respect to a drug for a more prevalent disease. This last aspect, like the severity of the target disease, is not directly significant for the assignment of the degree of therapeutic innovation of new drugs; it does, however, become important when allocating the economic resources of the NHS.

Criteria for ranking therapeutic innovation

In order to assign the degree of therapeutic innovation to drugs belonging to the three classes of target disease severity, the following aspects are taken into consideration: (**1**) the availability of existing treatments and (**2**) the extent of the therapeutic effect. Each of these parameters presents three possible options in decreasing order of importance. The combination of the various scores makes it possible to attribute the degree of therapeutic innovation of a new drug (see figure 1).

1) The scores for availability of existing treatments are:

- (A) drugs for the treatment of diseases currently without adequate treatment (this is the case of many orphan drugs for the treatment of rare diseases) or developed for subgroups of patients with absolute contraindications (section 4.3 of the technical sheet) for the use of drugs already on the market and for whom the new drugs represent the only possible therapeutic option;
- (B) drugs developed for the treatment of diseases in which subgroups of patients are resistant or non-responders to the first line therapy (this is the case of anti-HIV drugs or of some anti-cancer drugs);
- (C) drugs for the treatment of diseases for which recognised treatments already exist.

To ensure recognition of new drugs developed for the treatment of diseases for which treatment is already available but which could present advantages with respect to existing therapies, score C was further divided into three subgroups, also in decreasing order of importance:

- (C1) **more effective or safer** drugs or drugs with a better pharmacokinetic **profile** compared to existing drugs;
- (C2) drugs representing a simple **pharmacological innovation**: for example, drugs with a new mechanism of action but with a therapeutic role similar to existing drugs;
- (C3) drugs representing a simple **technological innovation**: for example, new chemical substances or products obtained by means of biotechnology but with a therapeutic role similar to existing drugs.

In a first application of this method to EMEA[5] drugs, and so as not to penalise similar drugs that were authorised not long after the pioneer drugs of a certain class, a so-called “innovation window” of 3 years was considered, i.e. in the case of marketing a congener of a pioneer drug considered to be innovative, the same degree of innovation (see point 1 above) is attributed to the congener drugs authorised in the 3 year period immediately following the authorisation of the pioneer drug. A period of more than 3 years would give the congener technological or pharmacological innovation status, as it would concern a therapeutic framework at that point already sufficiently covered.

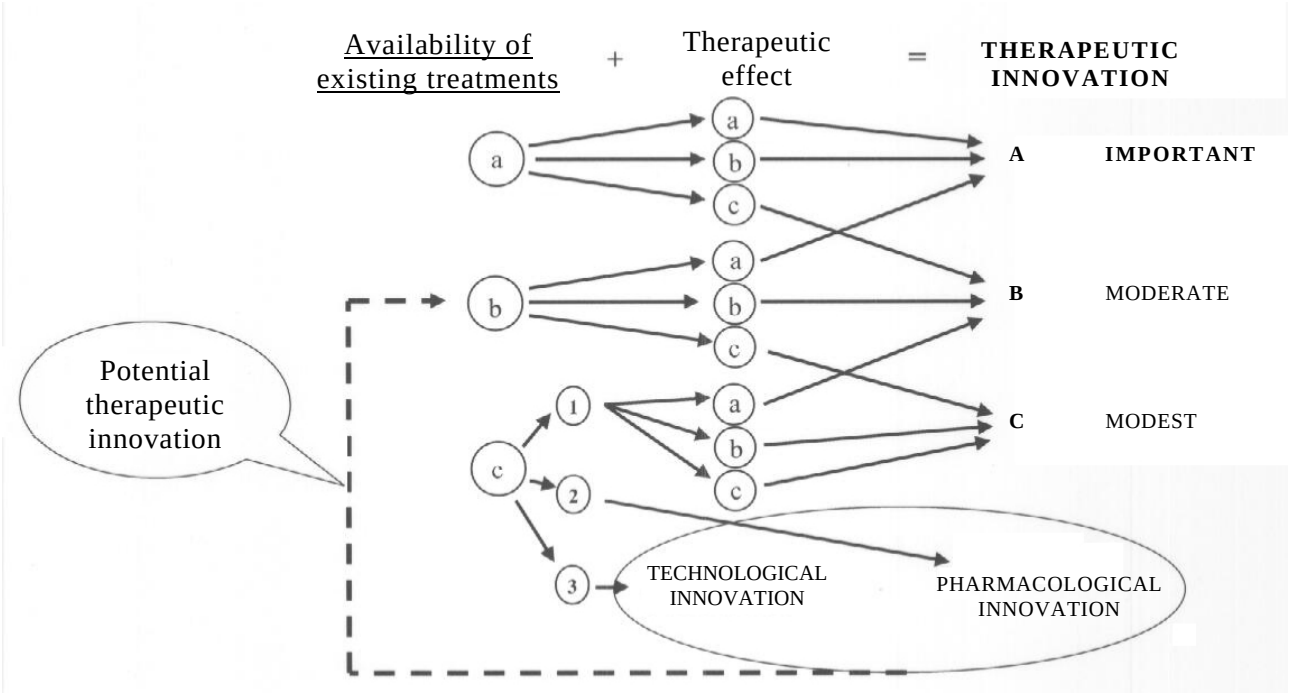
2) The scores for attribution of <u>the extent of the therapeutic effect</u> are:

- (A) greater benefits on clinical end-points (reduction in mortality and morbidity) or on validated surrogate end-points[1];
- (B) partial benefit on the disease (clinical or validated surrogate end-points) or limited evidence of a greater benefit (non-conclusive results);
- (C) minor or temporary benefit on some aspects of the disease (for example, partial symptom relief in a serious disease).

As can be seen from figure 1, the degree of innovation, whether important, moderate or modest, can be reached by various combinations of scores relative to existing treatments and therapeutic effect. The need is however felt for an improvement of the definition and detailed examples of the clinical benefits that are considered as major, partial and minor, and of the respective end-points. It is also necessary to better define the diseases that require further progress in terms of their treatment.

[1] "Surrogate endpoint: A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence"[6]

Figure 1. Algorithm for attribution of therapeutic innovation.



Potential therapeutic innovation

As stated above, a new treatment is **innovative when it offers the patient additional therapeutic benefits with respect to the options already available.** Drugs characterised merely by a new mechanism of action without offering a documented advantage in therapeutic terms can only be considered as **"pharmacological"** innovations**.** A **"technological"** innovation consists of molecules already available but obtained by means of biotechnological techniques or presented with new systems for releasing the active ingredient. **A pharmacological innovation** (new mechanism of action) cannot be considered a true therapeutic innovation, merely a **"potential therapeutic innovation",** which will be demonstrated as a true therapeutic innovation when evidence has been provided of additional therapeutic advantages with respect to treatments already available due to the new and different mechanism of action (for example, greater specificity on the target disease with fewer side effects). In the same way, **a technological innovation** can only be considered **a potential therapeutic innovation,** when evidence is presented that, for example, a new production method offers greater safety or a new release system allows greater compliance.
The criteria and the methods whereby the National Health Service can consider potential therapeutic innovation to be of interest are defined in Annex 1, which is an integral part of this document.

Limits of the algorithm

One potential limit of this algorithm is that the assessment of the degree of innovation of a new drug is based mainly on the efficacy and safety data available when the drug is (first) authorised. In particular, the assessment of safety must be updated on a regular basis for several years after the initial use of the drug in clinical practice; the same applies to the efficacy data, especially if supported by direct comparisons with other drugs in the same category. If this reveals a limit in the proposed method, it is nevertheless possible to subsequently modify (increase or decrease) the innovation score attributed to a drug on the basis of more evidence on its benefit/risk ratio.

Algorithm application examples

A series of examples are given below of attribution of the degree of innovation to various types of drugs.

- *tImportant therapeutic innovation (A)*
  This category includes orphan drugs for rare diseases. The important innovation is based on the consideration that these diseases are by definition serious and, in the majority of cases, without adequate treatment [A (severity of the disease) + A (availability of standard treatment) + A (extent of the therapeutic effect)]. The marketing of these drugs makes a first therapeutic option available for these diseases.

Another example is represented by drugs for the treatment of HIV infection. It is a known fact that numerous drugs have been available for the treatment of this disease for many years now. However, the phenomenon of viral resistance can considerably limit the efficacy of these drugs. The new anti-HIV drugs have been judged as being important therapeutic innovations (A+B+A) because the availability of new molecules increases the possibility of combining these drugs to overcome the problem of resistance.

- *Moderate therapeutic innovation (B):*

  This degree of innovation can also be achieved by means of various combinations of the individual scores. For example, a drug developed for a disease with no standard reference treatment (such as amyotrophic lateral sclerosis), but with a modest therapeutic effect (C) reaches a moderate degree of innovation (B). In this case, the assessment may be optimistic, but could be justified by the consideration that it is a drug for a disease without adequate treatment on which it has some effect, albeit modest. The same moderate degree (B) of therapeutic innovation can be achieved by a drug indicated for a disease already adequately treated (C) but which presents a greater efficacy or a better safety profile with respect to the existing treatments.

- *Modest therapeutic innovation (C):*

  A drug developed for a subgroup of patients who are non-responders to the standard treatment (score B for the availability of standard treatment) but with a therapeutic effect considered to be modest (score C for therapeutic effect) represents a modest therapeutic innovation (C). In the same way, drugs developed for diseases already adequately treated (score C for the availability of standard treatment), but which are judged to be more effective and/or safe or as having a better pharmacokinetic profile than the existing drugs (C) achieve a modest degree of therapeutic innovation (C).

  This proposal is intended to be a means that can be used for admission to the reimbursement system and the negotiation of the price of a new drug. It should be pointed out that, for this purpose, attribution of the degree of therapeutic innovation represents one of the aspects that can be assessed. At the time of admission to the reimbursement system and price negotiation, the severity of the disease to be treated and the epidemiological diffusion (prevalence) of the disease for which the drug is indicated must also be taken into due account.

<u>Manufacturers intending to present a drug they consider to be a therapeutic innovation (from important to modest) are invited to supplement the relative dossier by documenting the position of the drug according to the algorithm on page 5.</u>

References

1) Garattini S, Bertelè V. Efficacy, safety and cost of new anticancer drugs. *BMJ* 2002;325:269-271.
2) Garattini S, Bertelè V. Efficacy, safety and cost of new drugs acting on the central nervous system. *Eur J Clin Pharmacol* 2003;59:79-84.
3) Garattini S, Bertelè V. Efficacy, safety and cost of new cardiovascular drugs: a survey. Eur J Clin Pharmacol 2003;59:701 -6.
4) International Society of Drugs Bulletins declaration 2001. http://www.isdbweb.org
5) Motola D, De Ponti F, Rossi P. Martini N. Montanaro N. Therapeutic innovation in the European Union: analysis of the drugs upproved by the EMEA between 1995 and 2003.*Br J Clin Pharmacol.* 2005;59:475-8.
6) Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001 Mar;69(3):89-95.

Annex 1

Criteria for conditioned admission to the reimbursement system of drugs representing a potential therapeutic innovation (version dated July 6 2007)

The range and criteria for conditioned admission to the reimbursement system of drugs with potential therapeutic innovation are defined as follows:

1) The drugs must be potentially innovative, with the intention of making them promptly available for specific categories of patients for whom they may represent a therapeutic advantage, even though not yet fully demonstrated.

2) An essential aspect for conditioned admission to the reimbursement system is that they be considered of interest for the National Health Service in terms of the disease for which they are intended.

3) The drugs are admitted to the reimbursement system establishing the conditions and deadlines by which studies or research must be carried out for a precise identification of their therapeutic role.

4) The elements supporting this "conditioned admission" to the reimbursement system must be identified in a structured technical document presented by the Manufacturer, establishing:

   a) the therapeutic requirements that the drug satisfies (e.g. patients resistant or intolerant to standard treatments);
   b) the potential additional therapeutic benefits of the drug with respect to the options already available (e.g. better treatment compliance, greater tolerability;
   c) the open questions as regards the classification of the drug as therapeutically innovative;
   d) the research that will be carried out to provide answers to questions not yet resolved.

5) The additional studies or evidence can emerge from the commitments established by the EMEA in approving the drug or be proposed independently by the Manufacturer itself. In both cases, the time span must be reasonably limited (e.g. not more than two or three years). The objectives and the type of the studies are proposed by the Manufacturer and their relevance is assessed by the CTS.

6) The above-mentioned studies are the responsibility of the applicant Manufacturer, including the supply of drugs to be used, while for the remaining patients, not included in the studies, the drugs are covered by the NHS reimbursement system.

7) Any extensions of the indications approved by the EMEA during the period of conditioned admission to the reimbursement system will be dealt with separately and will be considered

irrelevant as regards application of the conditioned admission, unless taken into consideration at the start of the procedure.

8) If the deadline is reached without achieving the foreseen results, the conditions of admission to the reimbursement system will be re-assessed.

9) It would appear essential to consider the health-care effects deriving from the re-assessment of the conditions of admission to the reimbursement system made on the basis of the result of the studies carried out.

10) The criteria listed in this Annex are an integral part of the AIFA document on therapeutic innovation. **Manufacturers intending to present a drug they consider to be a potential therapeutic innovation are invited to supplement the relative dossier with items a), b), c), d) of point 4 of this Annex (see box).**