bit
Drug and Therapeutics Bulletin of Navarre. Spain
VOL 15, No 3 JUNE 2007

New drug evaluation. The experience of the Spanish Mixed Committee on New Drugs Assessment (MCNDA)

The information available on the efficiency and safety of new medicines is limited and almost exclusively comes from the clinical trials carried out for authorization purposes. These trials may guarantee the quality, safety and efficiency of the products but do not evaluate their role in therapeutics in comparison with other available alternatives. To reach this aim there should be objective and independent information available about new medicines from evidence-based drug evaluations carried out with a systematic, rigorous and transparent methodology.

The mixed committee of new drugs assessment set up in 2003 is made up of the individual committees of Andalusia, Basque Country, Catalonia Health Institute, Aragon and Navarre. Its principal aim is to evaluate the degree of therapeutic innovation in the commercialization of new drugs in comparison with what is already available on the market and thus be able to provide specific recommendations to the health professionals about them. This committee has a Normalized Working Method which guarantees that the new drugs evaluation processes are carried out in a homogeneous way and with consensus among the different constituent committees. The degree of therapeutic innovation of each new drug is determined in accordance with criteria of efficiency, safety, treatment and cost. A classification is then assigned within a range of five categories by reaching a decision algorithm.

Introduction

The high number of new drugs that come onto the pharmaceutical market each year and the wide exploitation made of these can have important clinical and economical implications for health systems[1]. Results of some studies on prescriptions of these new drugs reflect a growing exponential in number which comes about shortly after authorization is given and this does not seem to be related to real efficiency or therapeutic contributions[1,2]. Moreover, a wide range of uses are made of the drug which cannot be solely explained by therapeutic needs.

The International Society of Drug Bulletins (ISDB), which includes the main independent bulletins that gather information about new drugs, has defined "therapeutic innovation" in terms of comparative benefit, as distinct from commercial innovation and/or technological. It is believed that treatment represents "therapeutic innovation" if it offers advantages or benefits for patients when it is compared with the existing optional therapies in use. Thus, in order to properly establish the level of therapeutic innovation which a new drug provides, it becomes decisive to jointly evaluate the available evidence about its efficiency, safety and expediency. In addition, both quality and cost factors should also be taken into account[3].

By and large, the drugs which have been given authorization over these last few years have only provided potential advantages related to their pharmacokinetics and/or to their posology and method of administration ("me-too" drugs), which, in principle, would mean innovations of scant relevance compared to those already in existence.

Of the 10-20 drugs authorized each year in Spain, to be used in the area of Primary Care, few of these offer any real added value over those already marketed. However, their wide range and higher cost than the existing drugs becomes one of the main causes for the increase in public expenditure in pharmaceutical costs within the Public Health System.

In some cases, the launching of new drugs onto the pharmaceutical market only serves to increase a level of uncertainty among the practitioners in their daily medical labors. They have a wide range of drugs available which are often quite similar in chemical and therapeutic value, with little difference between them and often backed up by limited objective research[1]. New drugs tend to have less information about their efficiency and safety than existing ones, in spite of the fact that there may be abundant literature and clinical experience on their use[4].

Information available at the approval stage of new drugs often only comes from the clinical trials carried out in order to get the authorization procedure. Such trials are often made with small sample sizes, of limited duration and with pre-selected patients who may not represent the target population for the drug. Consequently, within the sphere of safety it does not allow potential adverse effects of slight prevalence to be identified, nor of course, those of long-term side-effects and in general they lack sufficient external validity. Thus, the authorization process for drugs in directed at guaranteeing their quality, safety and efficiency, without really evaluating their effectiveness or establishing their role in therapeutics in comparison with the alternative therapeutics already available.

The need to update knowledge about new drugs, along with the scant availability of time for their evaluation makes it imperative to have sources available that can provide objective independent information about them and from a perspective in which they will be used[4]. Consequently, it is important to carry out an evaluation of the new drugs, within a systematic methodology, based on scientific evidence and through a transparent, rigorous scientific process[4].

Background

The gradual creation of different Evaluation Committees for New Drugs in Spain responds to the need for having instruments at one's disposal in order to demarcate the boundaries between therapeutic innovations from those which merely exist for commercial purposes. Earlier, there had been other initiatives of national and international kind with a methodology and similar objectives and these have served as a reference in the development of the activities of the committees[4].

In 2002, after several years of working independently on the evaluation of new drugs, three of the committees –those of Andalusia, The Basque country and Catalonia– came together to share their experiences since they shared common methods and aims. Their aim was to unite their strengths in order to improve the quality and consistency of their shared activities. January 2003 saw their first meeting take place and this would soon become known as The Mixed Committee on New Drugs Assessment (MCNDA), The three initial committees soon expanded into five in total when Navarre and Aragon regional committees also joined up with them[4].

After organizing several work sessions about the techniques to be used, much progress has been made in creating a common policy about the diffe-

rent methods of evaluation used by the different committees of MCNDA. This has given rise to a Normalized Work Procedure with the common aim to improve transparency and contribute rigor to the process and to reduce inconsistency so as to ease reproduction. This Normalized Work Procedure serves as a reference for all the member committees of MCNDA and establishes the guidelines for the elaboration of evaluation reports, the procedures and datelines for reviews and for validation and revalidation. Thus, the evaluation process is made in its totality within a coordinated and agreed form among all the committees[4].

The setting up of MCNDA and the development of a common Normalized Work Procedure has allowed criteria to be unified with regard to the methodology for the evaluation of new drugs as well as to increase the number of evaluations carried out. It also means that the MCNDA is subject to a continuous evaluation process, as well as to renovation, updating and improvement, both with regard to the Normalized Work Procedure as well as to the development of new projects and initiatives related to the evaluation of new drugs. Among these new projects, information directed at the patients elaborated by CADIME (Andalusia Drug Information Center) for AETSA (Andalusia Agency for Health Technology Assessment) and critical valuation on the advertising material of the pharmaceutical laboratories related to new drugs (elaborated and edited by MCNDA from The Basque Country and Navarre[4].

Aims and methods

The five committees which make up MCNDA at present share the common aim of strengthening selective and independent information about the new drugs as a medium to improve supportive quality through the transmission of knowledge to the health professionals. Its function is to analyze and evaluate the therapeutic benefits that might come from new drugs within the pharmaceutical range on offer at present in line with available scientific evidence and offer specific recommendations to the professionals directly involved within their sphere of influence for the correct usage of same.

The aim is to provide answers to the main questions raised by the introduction of a new drug. Is it more efficient than others already on the market? What do we really know about its safety level? How much will it cost the patient and society in general? Is its use relevant? Are there any particular circumstances that could condition its use?

The different committees which make up MCNDA can count on the help of a multi-discipline team with a similar composition. Thus, there are normally hospital pharmacists and primary care pharmacists, doctors and documentalists, who have received specific training for this task as well as

The MCNDA is made up of the individual committees of Andalusia, Basque Country, Catalonia, Aragon and Navarre

experts in other disciplines such as epidemiology and public health, health technology assessment, pharmacovigillance, etc[4].

Their work range is confined to drugs authorized by the Ministry of Health which, since they are being financed by the National Welfare System of Health, are guaranteed immediate commercialization. Within this field of work are included not only the drugs themselves but also possible new indications, new associations and, sometimes, new methods of administration and new pharmaceutical forms of drugs that are already available. In addition the work field takes drugs for diseases requiring a hospital-based diagnosis, whose natural range of use lies in primary attention. Priority in the choice of drugs to be assessed is agreed on depending on their impact on prescriptions and bearing in mind their interest and relevance within the field of influence of each committee[5].

To facilitate the internal working of MCNDA, there exists a link-up group made up of representatives of each committee, who come together from time to time for workshop sessions. There is also a follow-up electronic sheet which is updated periodically as well as a web page with restricted access which helps to maintain a follow-up on the different assessment processes and to facilitate coordination between the different committees5. Up to now, communication among the different groups has mostly been held through e-mail and by telephone, and as to date, with quite satisfactory results[4].

There is a Normalized Working Method to evaluate and classify new drugs into five different categories

Methodology for the assessement of new drugs[4-6]

Identification of new drugs

Sources used as priority forms by MCNDA for the identification and assessment of new drugs are primarily drugs authorization updates rubber-stamped by the Ministry of Health and the list of drugs financed by the Spanish National Health Service, as well as the launching of new drugs by the pharmaceutical industry.

Selection of the gold standard

The selection of the comparable or reference drug to be compared with the possible advantages of the new drug is made in agreement with the algorithm shown in Fig. 1. To do so, the recommendations which appear in Practice Guidelines or Pharmacotherapeutic Guidelines of reference as well as other independent sources of information of a recognized prestige are considered.

Literature review

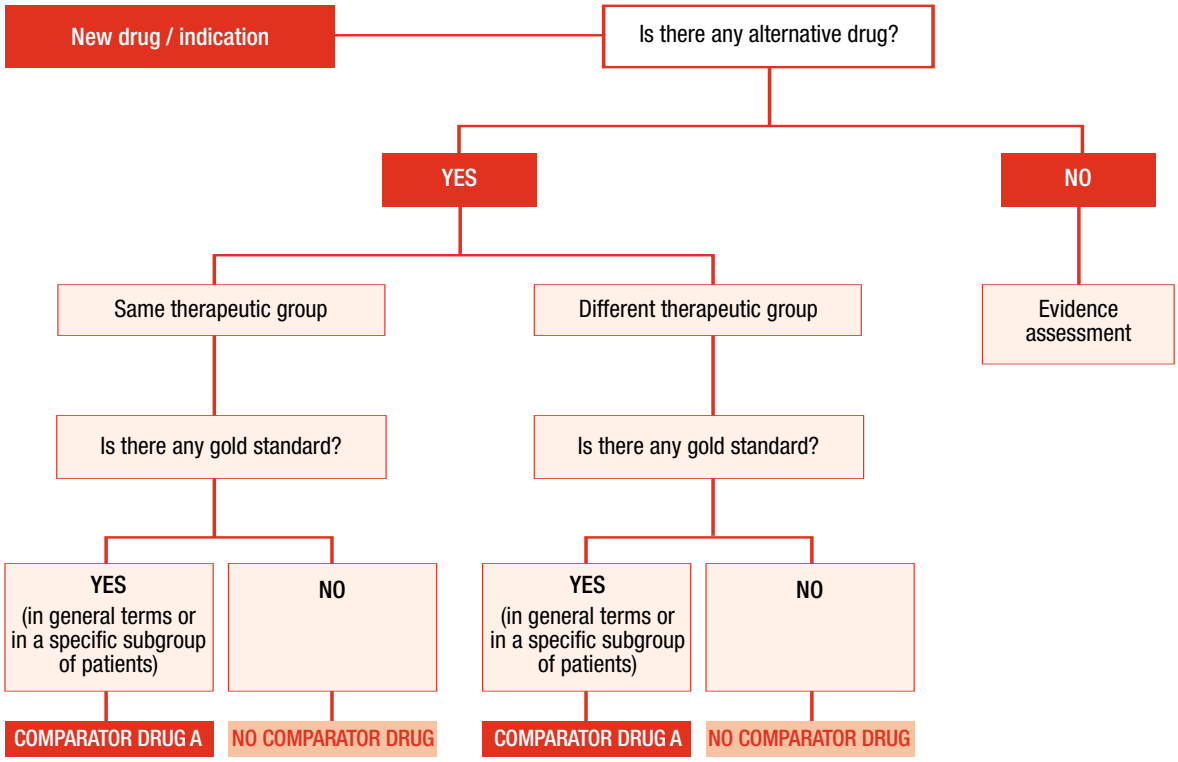
Literature search about new medicine is carried out in a systematic way for each of the drug authorized indications which are to be evaluation objects.

Product Information and the Authorization Technical Report (European Public Assessment Report) (EPAR), are useful to find out the approved indications and to locate clinical trials made for the authorization of the drug. Likewise, this constitutes a valuable source of information on aspects such as: counter-indications, precautions, interactions, etc. These documents can be obtained through the Spanish Drug Agency, the European Medicines Evaluation Agency (EMEA), Opinions and European Public Assessment Reports, Food and Drug Administration (FDA), Centre for Drug Evaluation and Research) and/or other evaluation agencies or indeed, from the pharmaceutical laboratory responsible for the development or commercialization of the product.

Randomized clinical trials constitute the principal source of information to evaluate the efficiency and safety of a new drug. Observational studies can be very useful to widen the information related to safety. When it is considered to be justified, other kinds of studies (uncontrolled trials) may be employed if they can provide relevant information about the drug. In general, the studies are selected on the basis of their methodology quality and in a priority manner they are published in complete form in medical journals.

As a complementary means, other evidence-based documented sources may be used, such as: Practice Guidelines, systematic reviews, meta-

Fig. 1. Algorithm for the selection of comparator drugs.



analyses, etc; as well as review articles which for their quality and/or approach may be useful for the evaluation of new drugs: Drug Evaluations from Drugdex® or Micromedex®, independent bulletins and drug evaluation reports) (Table 1).

The principal consulting sources to carry out literature research are: Medline (including PubMed), Iowa Drug Information Service (IDIS), Cochrane, Embase (Drugs and Pharmacology), Reactions and ADIS. In those cases where it is deemed necessary, the use of search filters may be considered in order to get to particular data base material so that location of existing randomized clinical trials is made easier.

Before making any kind of evaluation report, additional literature that is deemed relevant is requested from the pharmaceutical laboratory that is commercializing the drug. Particularly, those clinical trials which may not have been entirely published or others that may be difficult to attain through the normal channels.

Both new drug categorization and reports' contents are carried out with consensus among the five constituent committees

Analysis and evaluation of new drugs

After the search and selection of literature, a critical appraisal is made of the articles by way of a value judgement, analyzing the quantity and quality of the available scientific evidence in search of the possible generalization, relevance and clinical impact of the results. In order to assess the internal validity of the clinical trials and the relevance of the results, Jadad's scale[7] is then applied.

In order to establish its external validity and use in clinical practice, a questionnaire is used that allows an analysis to be made of the suitability of the comparator drugs, the endpoints, the patients' inclusion and exclusion criteria as well as other questions.

Available evidence is summarized in a Table which includes all the most relevant aspects of each of the clinical trials analyzed, following a format adapted from The Scottish Intercollegiate Network[8], in which appears the type of study, the aims, the population (criteria of inclusion y exclusion), the endpoints, the outcomes effect size, p-values, confidence intervals), score in Jadad's scale, etc.

The criteria used to establish the benefits of the new medicine as opposed to the available alternatives are: efficiency, safety, applicability (the model and form of administration) and the cost. These criteria are combined with the decision algorithm to assign a final qualification to the drug with regard to its therapeutic novelty (Fig. 2). The assigned qualification can fit into one of five established categories and it should be agreed on and evaluated by all the committees that make up the MCNDA (Table 2). When the drug shows several approved indications, it may be given different qualifications when it is felt that the available evidence justifies this action.

It is felt that a new drug is more efficient than other alternative therapeutics when the comparative studies have adequate internal and external validity and significant improvements are shown in the resolution of health problems in acute conditions or in the reduction of mortality and/or an improvement in the quality of life in chronic conditions. In terms of safety, it is understood that the drug provides advantages when the studies show significant reductions in the frequency of side effects which limit the use of the previously available alternatives. When it is felt pertinent, other aspects of new drugs will also be evaluated that could improve the quality of life of patients and/or facilitate treatment compliance: posology, method of administration, treatment duration, etc., as well as how its profile of interactions with other drugs or food.

The evaluation report also includes economic data-references to treatment costs both for the drug under evaluation as well as all the comparator

Table 1. Bulletins and other useful sources for the evaluation of new drugs.

Title	Website
Drug and Therapeutic Bulletin	http://www.dtb.org.uk/dtb/index.html
Medical Letter on Drugs and Therapeutics	http://www.medletter.com/
La Revue Prescrire	http://www.prescrire.org/
Midland Therapeutic Review and Advisory Committee	http://www.keele.ac.uk/depts/mm/MTRAC/
National Institute of Clinical Excellence	http://www.nice.org.uk/
Dialogo Sui Farmaci	http://dialogosuifarmaci.it/

Table 2. Qualification categories for new drugs according to their innovation therapy (MCNDA 2007)

Categories		Definition
0	Not possible to assess: Insufficient evidence	Available evidence is insufficient or inconclusive, or lacks good quality clinical trials including an adequate comparative drug.
1	No therapeutic innovation	The new drug has no added value over other drugs which are already available in the market for the same indication.
2	Some added value in specific situations	The new drug may have an added value in a particular condition or patient subgroup.
3	Modest therapeutic innovation	The new drug provides more posology comfort or it lowers treatment cost.
4	Important therapeutic innovation	The new drug provides an added value in terms of efficacy or safety compared to the available therapeutic alternatives for the same indication or condition.

drugs under consideration as well as those drugs felt to be of interest. In principle, the method of economic analysis used will be the comparison of costs of the drugs. However, from time to time complementary pharmacoeconomic studies will be made. In acute conditions the global cost of treatment will be determined, while in the case of chronic treatment, the daily cost will be calculated.

It is important that the position of the new drug be clearly established in therapeutic terms compared with the gold standard and that a comparative analysis be made of the evidence that justifies this qualification standard proposal. Whenever possible, explicit recommendations will be included for the use of the drug under evaluation as well as a justification for its use. Whether there are comparative studies or not will also be commented on and highlighting aspects of the drug which have insufficient information and which might be cleared up with a wider clinical investigation.

The content of the report is structured in a standard format, organized in different sections which deal with the following aspects: name of the medicinal product, trade mark, manufacturer, date of issue, therapeutic group, date of authorisation, approval procedure, indication, mechanism of action, pharmacokinetics, posology, methods of administration, efficiency, safety, economic information, alternatives available, and comparable reference drugs and its role in therapy. In addition, an assigned qualification as to its level of therapeutic innovation will be included and a summary of the most outstanding aspects. The literature references used will be inserted in the text of the report and these can be found at the end of the report, in line with uniformity norms of biomedical publications of Vancouver.

Evaluation of new indications, pharmaceutical forms and associations of commercialized drugs

In principle, evaluation of new indications, pharmaceutical forms or associations of drugs already commercialized will be made according to the standard procedure and in line with the decision algorithm (Figure 2). However, content of the report could be more reduced, focussing on those aspects of greater interest or relevance. In this way, comparative studies would be made as against the pharmaceutical forms available earlier (in the case of new pharmaceutical forms) and against the components by separation and/or other similar associations (in the case of new associations).

Exceptionally, when dealing with a new pharmaceutical form which does not mean any changes in the administrative method or in the therapeutic form and there are no comparative clinical trials, pharmokinetics trials will be required to guarantee its bioequivalence. Furthermore, evaluation of new associations of drugs which are the first choice in the authorized indications, may be focussed on the criteria of posology comfort and cost, both being independently evaluated.

Validation Process

The evaluation reports of new drugs made by MCNDA become the object of a review and validation process on the part of the incorporated committees. In this process the documentation provided by the evaluation committee (the report text, the table of proofs, the literature, comments), is analyzed, determining the modifications and proposals that it deems fit. These changes are accepted in total or partially by the evaluation committee in order to produce the text of the final report, which should be agreed with by all the committees, especially with regard to reference comparators and the qualification assigned to the drug. Once a consensus is reached and the definitive report is sent out, this is adapted and spread around by each one of the committees within their respective regional territories.

Re-evaluations

The evaluation of the new drugs is made during the process of their commercialization and it depends on information whose validity could become limited with the passing of time. The appearance of new scientific evidence which would strengthen the modification of the content, conclusions and/or recommendations that appear in the report, could determine the need for carrying out a re-evaluation of the same drug by the

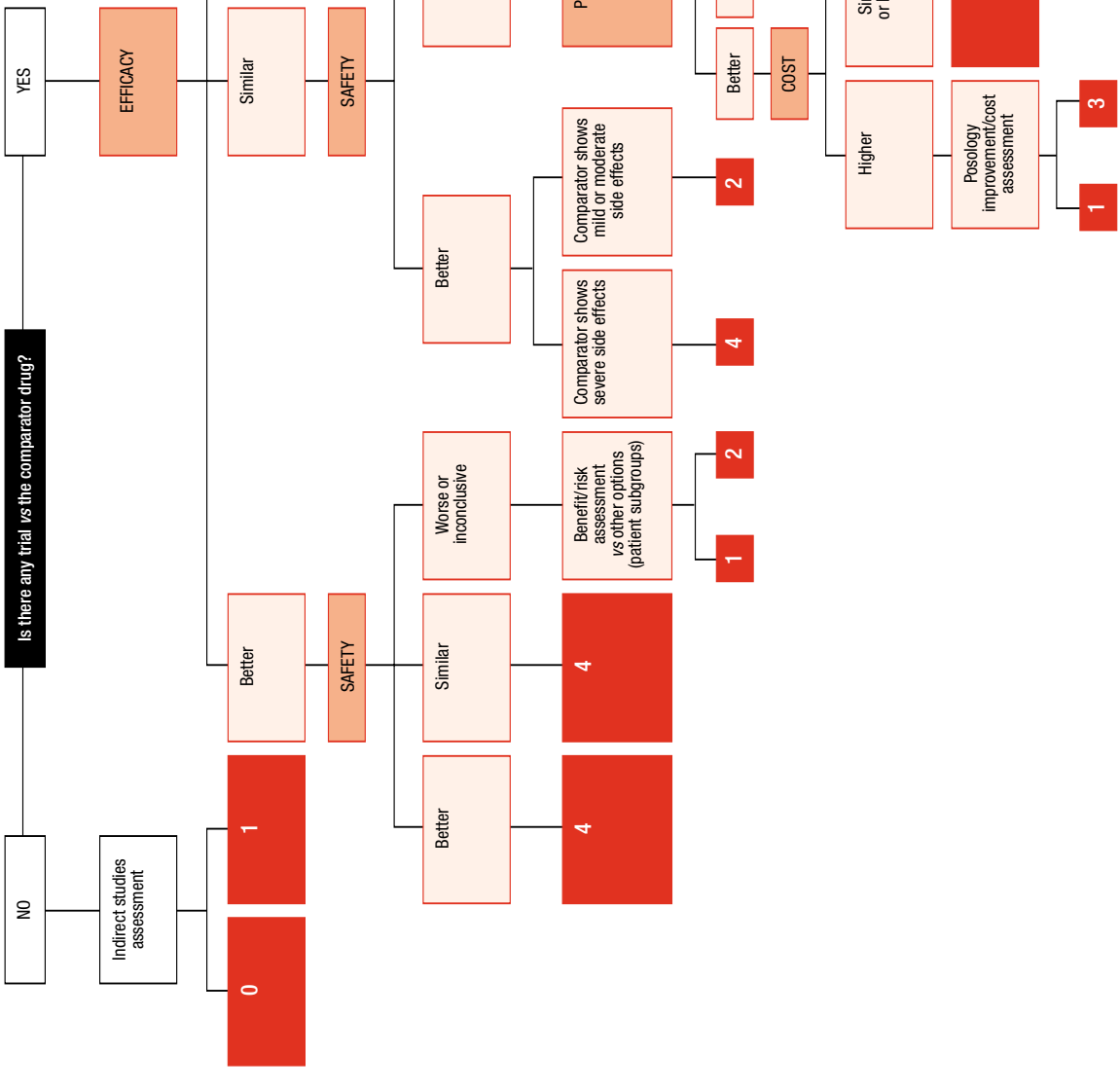


Fig. 2. Algorithm for the classification of new drugs according to their therapeutic innovation.

MCEND. In line with this, action would be taken through one's own initiative as well as from requests or demands from the professionals in the health service and/or from the pharmaceutical industry. To this end, there is form available which should be filled in by whoever requests the re-evaluation, and the required documentation should be given in.

The re-evaluation will be carried out by the committee which had initially worked on the evaluation report, although it will also be reviewed, accepted and validated by all the member committees of the MCNDA. In principle an answer will be given –favourable or unfavourable– to all the re-evaluation requests received, although only those that are considered justifiable will actually be carried out.

The re-evaluation report of a drug may be carried out in an abbreviated way, highlighting the most relevant or conflictive aspects in relation to the content of the initial report. When it is deemed necessary, expert assessment may be sought or consulted in organisms and institutions other than the MCNDA, such as, for example, the National Network of Pharmacovigillance.

Final considerations

The creation and working of MCNDA constitutes an innovative organization in Spain and provides greater transparency and homogeneity for the evaluation process of new drugs.

Likewise, it is hoped that the adoption of a transparent, reproducible and homogeneous process which has been agreed on by different groups, will reinforce the credibility of the recommendations made by MCNDA among the laboratories and other health professional bodies.

REFERENCES

1. Prescripción de nuevos medicamentos. Bol Ter Andal 2001; 17(5): 18-20.

2. Aza Pascual-Salcedo M et al. Velocidad de incorporación de nuevos medicamentos en la práctica clínica. Comunicación presentada EN: XI Congreso Nacional de la SEFAP. Burgos, 25-27 de octubre, 2006.

3. Declaración de la Sociedad Internacional de Boletines de Medicamentos (ISDB) sobre Avances en Terapéutica con Medicamentos. París, 15-16 de noviembre de 2001. Disponible en URL: http://66.71.191.169/isdbweb/pag/spa.php

4. Catalán A et al. La experiencia del Comité Mixto de Evaluación de Nuevos Medicamentos (CMENM). Farm Aten Prim 2006; 4(extra): 7-17.

5. Procedimiento Normalizado de Trabajo del Comité Mixto de Evaluación de Nuevos Medicamentos de Andalucía, País Vasco, Instituto Catalán de la Salud, Aragón y Navarra (7ª versión, septiembre 2005). Farm Aten Prim 2006; 4(extra): 19-29.

6. Procedimiento Normalizado de Trabajo del Comité Mixto de Evaluación de Nuevos Medicamentos de Andalucía, País Vasco, Instituto Catalán de la Salud, Aragón y Navarra (8ª versión, en prensa).

7. Jadad AR, Moore RA, CarrolD, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12.

8. Scottish Intercollegiate Network. A guideline developers' handbook. Completed Evidence Table. Disponible en: http://www.sign.ac.uk/guidelines/fulltext/50/compevidence.html (last accessed: 03/04/2007).

Servicio Navarro de Salud
Osasunbidea

ISSN
1138-1043

INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T +34 848429047
F +34 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

WEB PAGE
http://www.cfnavarra.es/WebGN/SOU/publicac/BJ/sumario.htm