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# TABU

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## Summary

## Summary

**Hannes Wahlroos**
Director General, Professor
National Agency for Medicines

# A remedy for the problem of medicines' availability

Contributions to this column and to other public columns a year ago addressed the availability of medicinal products in Finland. It transpired that within ten years medicines authorised for marketing had, in fact, fallen from having been almost 100% available on the market to 77% of all valid marketing authorisations. The situation of medicinal products within the EU centralised approval system was found to be even worse.

Improvements have been made in monitoring the availability of medicinal products by the NAM in Finland. According to the information from last August (see p. 62 the *ex tempore* column), however, the situation of availability has in fact become worse. Over a third of the medicinal products with valid marketing authorisation are not actually for sale in Finland. The situation is partly explained by the fact that during the last couple of years the NAM may have processed a great number of marketing authorisation applications within the stipulated time limit for processing, and that, consequently, the applicants have not yet managed to bring their products on to the market. Nevertheless, the list of "medicinal products not available" unfortunately also contains a large number of items from even earlier years.

There are many reasons for the prevailing circumstances, not the least important one of which is the fact that the EU allows marketing authorisations to be applied for without any obligation for the applicant to ensure the availability of the medicinal product on the market. Member states with smaller pharmaceutical markets are particularly those which suffer most. Similarly, countries with well operating authorisation procedures in place also suffer, since that makes it attractive for the marketing authorisation applicants to use the authorisation approved in such a country only as a stepping stone towards approval in other countries.

It is therefore excellent news for the pharmaceutical markets and authorisation procedures in Finland and the EU that the EU Directive relating to medicinal products for human use has been amended by a new Directive with regulations with the following contents, for example[1]:

"*Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.*

*When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.*"

These regulations will be included in the Medicines Act and will come into force in Finland by the 30th of October 2005. According to the statements emanating from within the pharmaceutical industry itself, the purpose of applying for a marketing authorisation is to make the medicinal product actually available on the market.

The new regulations are helpful to the pharmaceutical industry and the authorities insofar as unnecessary preparations and processing of applications, the duties associated with the maintenance of marketing authorisations, and the costs associated therewith, can be avoided with some advance consideration. An authorisation system should have a purpose which is fulfilled; this is an old principle and one even endorsed by the EU itself.

[1]) Directive 2004/27/EC of the European Parliament and of the Council [Article 24(4) and 24(5)]; OJ L 136, 30.4.2004, p. 43.

## Summary

**Tarja Rautanen**
D.Med.Sc., Paediatrician
Jorvi Hospital

# Treatment of acute diarrhoea in children

*Acute diarrhoea still remains among the most common diseases in children in Finland resulting in around 3,500 hospitalisation periods each year (1). There has been a noticeable reduction in the occurrence of fatal diarrhoea in Finland during the last decades. Nevertheless, as late as between 1986 and 1995 nine children originally in good health died of diarrhoea in Finland (1). Over half of the deaths occurred at home or on the way to the hospital, underlining the importance of effective care at home and correct timing in seeking help.*

As in other developed countries, the majority of cases of diarrhoea in Finland are caused by a virus; bacterial diarrhoea is rare (2). Antibiotics are therefore seldom of use in the treatment. Dehydration is the most severe complication of diarrhoea; treatment of diarrhoea is therefore aimed at the prevention and treatment of dehydration. Fluid therapy is given independently of the causes of the diarrhoea. Oral rehydration solution, which has been in use for over 30 years, has revolutionised the treatment of diarrhoea and saved millions of children world-wide. The introduction of the oral rehydration solution in Finnish hospitals, and the uninterrupted feeding practices adopted in the 1980's, together with good treatment results, reduced the hospitalisation periods by one day during 1986–1995 (1).

Concern about the inadequate treatment of diarrhoea in children has been expressed in many developed countries. In England the treatment of more than a third of the children has been based on inadequate instructions given by the family doctor for the treatment of diarrhoea (3). In the USA, over half of paediatricians did not follow the instructions of the AAP (American Academy of Pediatrics) on the use of the oral rehydration solution and uninterrupted feeding practices (4). In the UK, over 50% of pharmacists gave incorrect instructions to parents about the treatment of diarrhoea in their children by recommending antidiarrhoeal agents and advising mothers to stop breastfeeding for the duration of the diarrhoea (5).

Subsequently, a retrospective survey of childhood diarrhoea and home treatment practices was carried out in Finland in 1996 based on the catchment area of Espoo and its well-baby and maternity clinics. A total of 1,726 mothers and their 2,230 children under the age of 5 were interviewed. The survey showed that 37% of the children were given a rehydration solution (70% in fact, if the disorder was severe enough for the child to be hospitalised), 55% of the children were offered normal or greater than normal size diets, and 7% of the children were put on a fasting diet during the diarrhoea. 74% of the chil-

***Table 1. Change of home treatment practices of acute pediatric diarrhoea in Finland*** *(Isolauri et al. 1989, Rautanen et al. 1998)*

| | *1978* | *1987* | *1996* |
|---|---|---|---|
| *Preadmission of ORS use rate* | *3 %* | *29 %* | *70 %* |
| *Use of antidiarrhoeal drugs* | *11 %* | *3 %* | *0.7 %* |
| *Fasting* | *67 %* | *53 %* | *7 %* |

***Main principles in the treatment of acute childhood diarrhoea***

- *Fluid therapy or prevention of development of dehydration and correction of any dehydration present*
- *Early feeding*
- *Use of probiotics*
- *Avoidance of antidiarrhoeal drugs*

dren who were being breastfed were offered breast milk more often than usual throughout the diarrhoea. The figures show that the home treatment practices are not optimal, but a distinct improvement has been made compared with 1978 and 1987 (Table 1) (6, 7). Not all mothers are aware of the importance of the oral rehydration solution and continued feeding. Instructions for the treatment of diarrhoea given by health centres, well-baby and maternity clinics and pharmacies are therefore of paramount importance.

## Fluid therapy

The prevention of dehydration should be started immediately at the onset of diarrhoea. The parents should offer their child greater amounts of fluid than normal (8). If the child is still being breastfed, the number of feeds should be increased, as breast milk is an excellent rehydration solution (8, 9). The best product to prevent dehydration is the oral rehydration solution available from pharmacies; water should be offered freely along with it. At the stage of prevention, mild juices, milk and soup are also appropriate drinks. Beverages with high sugar contents such as soft drinks should be avoided. Due to their high sugar contents these drinks have no rehydration properties; they cause osmotic diarrhoea instead and promote the development of dehydration. For the prevention of dehydration, the oral rehydration solution is administered at a dose of 1/2 dl per each diarrhoeal stool in children under 2 years of age, and about 1 dl per each diarrhoeal stool in children over 2 years of age (8). If the child is showing signs of dehydration, its degree should be established depending on the weight loss or clinical findings. The loss is overcompensated by giving 4/3 of estimated fluid deficiency within the subsequent 6 hours (10). The administration of plenty of fluids is continued thereafter similarly to the prophylactic practices of dehydration. The average duration of diarrhoea is 4.8 days (6); and the administration of plenty of fluids should continue throughout the diarrhoea.

In mild and moderate dehydration, fluid therapy with oral rehydration solution has been shown in several studies to be at least as effective as intravenous fluid therapy, or even superior, since the duration of diarrhoea in children on oral rehydration therapy is shorter and their weight gain is superior to those on intravenous fluid therapy (11, 12). Severe dehydration requires intravenous fluid therapy. Even then, oral fluid therapy should be introduced as quickly as possible after recovery from dehydration (8).

Consulting a doctor is recommended if the child exhibits distinct signs of dehydration, or the child is very restless or exhausted, diarrhoea and/or vomiting occurs very frequently, or blood is present in the stools. Diarrhoea in infants under 6 months of age calls for prompt consultation with a doctor because of the risk of rapid development of dehydration.

## Early feeding

Fasting was a common practice and part of the treatment of diarrhoea for a long time also in Finland. Several clinical studies have shown reduced duration of the diarrhoea and improved weight gain, once the children had started receiving full diets appropriate for their age immediately after the initial fluid therapy. Fasting and gradual reintroduction of food will lead to prolonged diarrhoea, impaired weight increase and damage to the mucous membrane (13, 14). Following recovery from dehydration, the child should be given energy-rich and easily digested food even more frequently than usual (8). Breastfeeding should also be continued throughout the recovery period (8, 9). Replacement products or milk products should not be diluted, and there is no need to put the child on to a milk-free diet (14, 15).

## Use of probiotics

The use of probiotics, or live microorganisms improving the wellbeing of the intestine, have been found to shorten the duration of acute diarrhoea (16, 17, 18, 19). Products containing Lactobacilli enhance the immune response of the intestine, they produce agents inhibiting bacterial growth and they interfere with the attachment of pathogens to the mucous membrane (16, 17, 20, 21). Probiotic therapy introduced at an early stage reduces the duration of diarrhoea by about a day. The recommended dosage consists of one tablet or a dose of Lactobacillus in powder form, or, alternatively, one dose of a sour milk product twice daily throughout the diarrhoea.

The probiotic therapy has been rapidly adopted by Finnish mothers. In the survey carried out in well-baby and maternal clinics in Espoo 44% of the children had received a probiotic product during the diarrhoea.

## Avoidance of antidiarrhoeal drugs

Antidiarrhoeal drugs are not a remedy for the actual complication of diarrhoea which is dehydration. Antimotility drugs (loperamide, opiates) depress intestinal peristalsis thus reducing the frequency of stools passage. They do not prevent the secretion of diarrhoeal stools or the development of dehydration. They make the assessment of dehydration difficult, because there is no weight reduction and the actual amount of stool is not visible. They may cause side-effects such as paralytic ileus and CNS symptoms which interfere with successful fluid therapy. These drugs should not be used in children, and their use even in adults has potential benefits only in temporary use, e.g. making a flight journey home possible. Adsorbing medicinal substances such as medicinal charcoal or bismuth are considered to adsorb the bacterial toxins which induce diarrhoea. In practice, the effect of these drugs is insignificant and they may be described as "stool cosmetics". They hardly cause any side-effects, but they may give a false impression of safety, result in negligence of fluid therapy and increase the price of treatment (22, 23).

The use of antidiarrhoeal drugs has never been a big problem (Table 1) in Finland compared with several southern European countries and

developing countries where the use of symptomatic drugs may be so high as to exceed 50%. In the survey carried out well-baby and maternity clinic in Espoo the use of symptomatic drugs amounted to only 0.7% (3). Two thirds of these drugs were obtained from abroad.

## Conclusion

The practices with regard to the treatment of childhood diarrhoeas in hospitals and at home have improved and largely follow the treatment recommendations of WHO. Information and awareness about the oral rehydration solution should be disseminated further, since its use should be close to 100% in acute diarrhoeal disorders both in the home and in hospital situations.

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## Summary

**Tiina Seppä**
Senior Researcher, PhD (Pharm)
National Agency for Medicines

# Clinical drug trials notified to the National Agency for Medicines in 2003

A total of 273 new clinical drug trials were notified to the NAM in 2003. Documents associated with clinical drug trials submitted to the NAM fall within the category of business secrets and professional secrecy (the Act on the Openness of Government Activities 621/1999). The processing of the notifications involves storing the key data in the data management system of the NAM. The NAM then uses the information contained in the database for its supervisory duties relative to clinical drug trials, in accordance with the Medicines Act and for the managerial and statistical compiling purposes relating to the trial reports.

In 2003, the pharmaceutical industry sponsored 187 (68%) of the new trials notified, whereas 86 trials (32%) were to be carried out without outside financing. Additional information was requested by the NAM on 127 trials (47%). Compared with previous years, the number of requests for additional information has remained fairly unchanged.

### Number of trials

The number of drug trials notified to the NAM has varied between 263 and 313 during 1994–2003 (Fig. 1). A clear majority of notifications in 2003 were made on trials at phase III, i.e. 41% of the total number (113 in all). The proportion of phase I trials was the smallest, i.e. 11% of the reports (30 in all). The number of phase II trials was 72 (26%), and of phase IV trials there were 58 in all (21%). The number of reports of phase II and IV trials received was slightly higher than the year before, but the variations were relatively small.

Of the trials notified during 2003, 7%, or 20 in number, were cancelled before the start. Up until the point of writing this survey, 6 trials had been discontinued on the initiative of the sponsor of the trial. Reasons for the discontinuation include a higher number of adverse drug reactions than expected, lack of efficacy of the trial product and redirection of the sponsor's resources towards other projects. One trial was also prohibited by the NAM due to insufficient data submitted in the notification regarding the trial drug used in safety studies in animals and relating to the pharmaceutical and – chemical properties of the trial product.

The trial notification should contain an estimate of the number of trial subjects. According to the prior information received, trials notified in 2003 will have a total of 10,763 subjects participating.

A review according to ATC categories (Fig. 2) reveals that the largest number of trials were reported on antineoplastics and immunomodulating agents (19.5 %). The second largest group consisted of drugs acting on the nervous system (16.0 %), followed by cardiovascular drugs (9.5 %), musculoskeletal system drugs (9.2 %) and drugs used in diseases involving the blood and blood-forming organs (7.9 %).

### Trial products

A review of the trial products involved shows that the majority of products were conventional synthetically manufactured medicines. According to the classification of the Agency, 52% of the trial notifications (142 in total) involved an already known medicinal substance

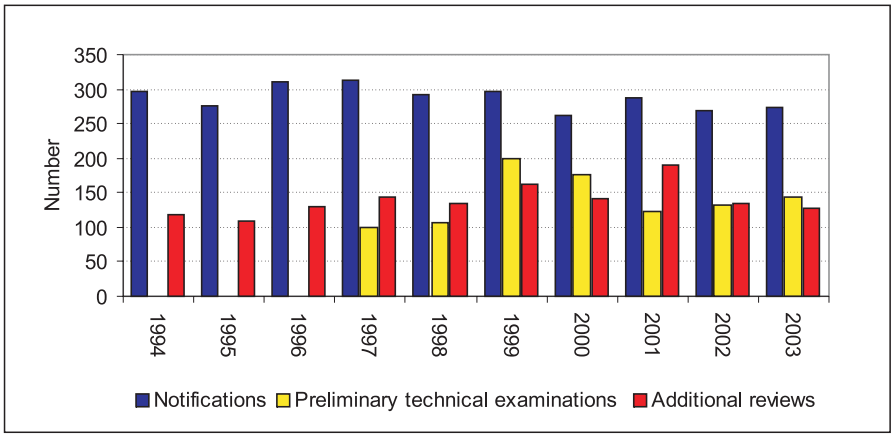


*Fig. 1. Numbers of trial notifications and complementary and additional reviews requested by the NAM. Prior to 1997, statistics of additional reviews requested in association with preliminary technical examinations were not recorded.*

with a marketing authorisation either in Finland or some other country. A total of 21 notifications (8%) involved a pharmaceutical innovation making use of biotechnology. Only one trial notified in 2003 involved gene therapy.

## Deficiencies discovered in the trial notifications

On receipt of the trial notification , the National Agency for Medicines may request additional information while the preliminary administrative review is carried out. Once the expert reviews are in, additional information may still be requested by the Agency as necessary.

The majority of the deficiencies detected in the preliminary technical review of the trial notifications involved the documentation on the manufacture and quality of the trial drugs. Documents on products without a marketing authorisation should include the data on their pharmaceutical and chemical properties, which were missing in 21 cases (8%). A review of the manufacture of the trial drug according to good manufacturing practices (a pharmaceutical manufacturing authorisation or a GMP certificate issued by the authorities) was missing in 24 cases (9%). Other deficiencies detected in the preliminary reviews include, for example, irregularities in the supplying of the trial drug to trial centres and in remitting the trial fee to the Agency, and the omission of details of the sponsor's agent or contact person. Two notifications contained no trial protocol at all. The processing of the notifications in these cases will not be started until they have been completed appropriately and all necessary information supplied.

The most common cause for requesting additional information after the completion of an expert review was an inadequate patient information leaflet or consent form. In 2003, requests were made for the patient information leaflet for 79 reports (29%) to be completed or corrected, while for 22 trial reports (8%) the consent form had to be completed or corrected. Stipulations for the contents of the consent form are found in the Medical Research Decree (986/1999). The deficiencies detected by the NAM have mostly involved technical details referred to in the Decree. A suggestion has often also been made by the Agency to include a reference in the consent form regarding the right of a foreign drug authority to examine the patient documents. The NAM in Finland has this right in accordance with the Medicines Act, but if the intention is to give the examination right to a foreign authority as well, a special reference needs to be made in the consent form.

Further common causes for requesting additional information in the notifications of 2003 included issues relating to the manufacture and quality of the trial product in 38 reports (14%) and issues relating to patient safety in 28 reports (10%). The requests for additional information on patient safety issues mostly deal with the performance during the trial of laboratory tests aimed at ensuring the safe use of the product (e.g. ECG, blood count, monitoring of liver and kidney function). The more rare requests for additional information dealt with the trial setting (13 requests, or 5%) or the statistical processing of the results (3 requests, or 1%).

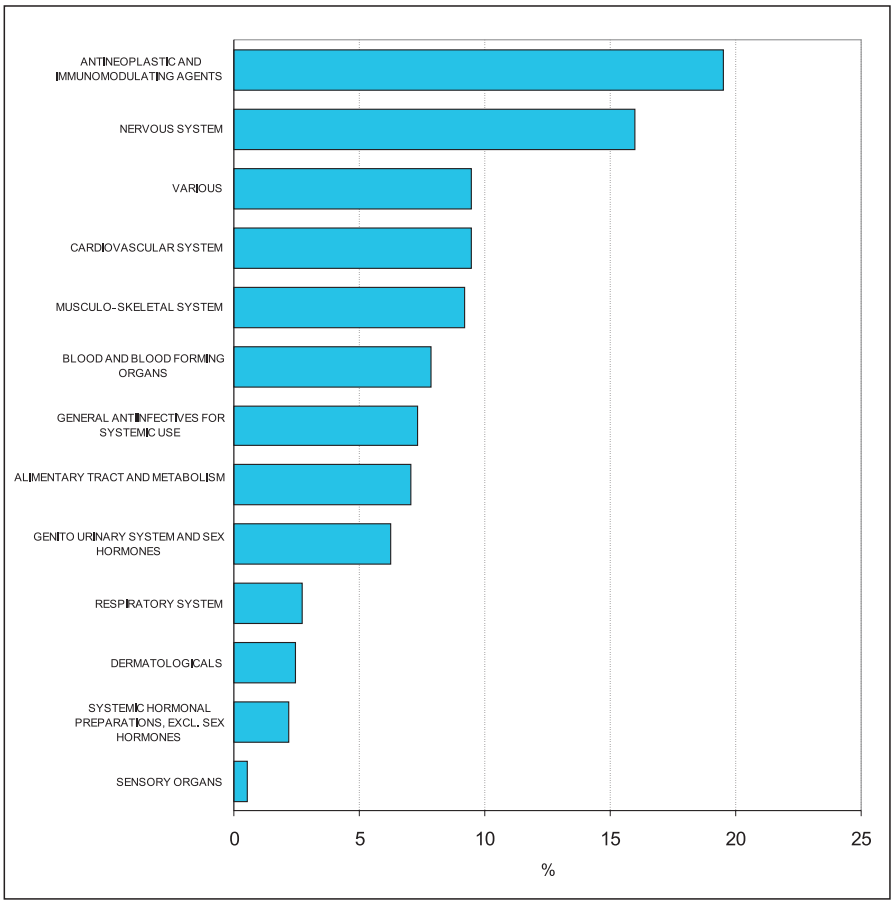


*Fig. 2. Division of the trial drugs into main ATC categories 2003*

## Reviews of trial results

The investigator and the sponsor are obliged to submit a review of the trial results to the Agency within a year following the end of the trial. This was previously stipulated in the Agency's regulation on clinical trials, but after a reform of the national legislation following the enforcement of the EU Clinical Trials Directive, the submission of reviews is now stipulated in an Act of the Law (Section 10h of the Medical Research Act). Reviews of results from 254 trials were submitted to the Agency in 2003. It is still the case that about 50% of investigators and sponsors do not send the requested reviews to the Agency until after receiving a written reminder. As the obligation to submit a review is now included in an Act of the Law, it is expected that researchers in future will remember to make a review of their trial results available to the authorities without a special request from the Agency.

## Summary

**Hannu Koponen**
Professor
University of Oulu

**Ulla Lepola**
Senior Lecturer
University of Helsinki

# The placebo in psychiatric drug trials

*Clinical drug trials are regulated by standards and principles with the aim of both safeguarding the patient safety and ensuring the faultless availability of reliable information about the object of the survey. In order to achieve the requisite power to detect a possible difference the latter requires survey groups and methods which are adequately defined and of adequate sample size. The use of a placebo group in clinical drug trials is as well founded as ever, and is especially important in conditions where the severity is associated with variation in time, or the possibility of a spontaneous recovery, or there is a significant proportion of subjective experience.*

The medical treatment of psychiatric conditions has over the past decade or more been considerably reformed, and improved tolerability and efficacy have been attained with the new alternatives of medical treatment for psychiatric disorders. Prior to launching on to the market, a new drug will need to undergo extensive clinical drug trials with the aim of surveying its efficacy, safety, tolerability and appropriate dosage range. In addition to using groups of patients receiving medical treatment with the active agent, these trials also use groups of patients receiving a placebo lacking any pharmacological effect. Nonetheless, not all clinical drug trials, e.g. trials surveying the pharmacokinetic properties and potential interactions, use a placebo group.

The first placebo-controlled clinical drug trial was carried out with streptomycin over fifty years ago, but the first trials of treatment including a placebo group date back to the end of the 1700s (Leber 2000). Nowadays clinical drug trials are regulated by various standards and regulations (Bardy 2000, Lääketietokeskus 2000, Lääkelaitos 2001) including ethical principles. The most important ethical principles are set out in the Helsinki Declaration of the World Medical Association (WMA 2001) according to which a new form of treatment needs to be compared with the best present method of treatment of the particular disease. This is not considered as excluding the use of a placebo in trials (Idänpää-Heikkilä 2001, International Ethical Guidelines for Biomedical Research 2002), and medical authorities in various countries actually require placebo-controlled clinical drug trials in reviewing the efficacy of new medical treatment. It is required by the European Medicines Agency (EMEA), for example, that in the most severe psychiatric conditions – such as schizophrenia, bipolar affective disorder, and severe depression – the efficacy of a new drug should also be demonstrated in trials in which the drug is compared with both the placebo and the active agent used at present to treat the particular disorder (EMEA 2003). Furthermore, for some psychiatric disorders there are no generally accepted current treatment methods available which would be both adequately effective and tolerated.

## Clinical drug trials in practice

The prerequisites for participation in a clinical drug trial are that it should be voluntary and that it should not involve any significant risks for the patient. For the latter reason, drug trials incorporate a detailed list of excluding factors, the most important ones of which for psychiatric disorders include the risk of suicide and the inability, associated with cognitive disorders, to understand the trial.

The suggestion of participation in a trial which could probably even harm the relationship between doctor and patient is considered problematic, but a recent survey shows that about three quarters of patients with even the most severe psychiatric disorder, schizophrenia, approved of clinical drug trials and did not consider the suggestion to participate in one to be harmful to their relationship with their doctor (Emmanuel and Miller 2001). Once patients have given their consent to participation in a trial they have the right later at any stage to withdraw from it without giving a reason and without any consequent effect of the withdrawal on their treatment (Lääketietokeskus 2000). After the withdrawal the patients will receive the conventional treatment usually given for their particular disorder.

## The structure of the drug trial

The most important issues under review in a clinical drug trial include the schedule of emergence of drug response, the extent of the response, and the relationship between the size of the dose and the response, and between the size of the dose and the number of adverse effects (Hummer et al. 2003).

A situation in which the new and the current conventional treatment are equally effective is a common end result in clinical drug trials

(Roland and Torgersson 1998). In this case only the presence of the placebo group will allow us to judge whether the therapies compared with each other are effective at all or whether any change possibly seen has been, for example, due to the patients' reaction to the trial arrangements. If the effect of the trial drug proves to be weaker than that of the control drug, the placebo group makes it possible to assess any efficacy there is, in any respect, in the new drug. But if the efficacy of neither the trial drug nor the active control drug differs from that of the placebo, the structure and/or the composition of the patient groups can be expected to be associated with some essential problems, or, alternatively, both drugs are ineffective. If, on the other hand, the trial drug and the placebo are equally effective, and the active control drug is distinctly more effective than these, the result can reliably be considered a negative proof of the efficacy of the new product. It should be borne in mind, however, that the difference in efficacy between the placebo and the active medicinal substance, according to meta-analyses of antidepressants, for example, is on average about 25% (Roland and Torgersson 1998). In this case, a sufficiently large sample of patients is required for proof of efficacy.

One of the key factors in ethical evaluations of trials is, in fact, assessment of the sample size. An inadequate sample size may lead to an incorrect negative result (error of type II), in which case the difference between the therapies would not be seen despite the fact that there is one in reality. An excessively large sample size would, on the other hand, expose patients unnecessarily to a trial therapy or to a placebo. At the stage of the trial design, assessment of not only the chief response parameters but also of the trial setting (e.g. parallel groups or an alternating trial) and the optimum sample size is made.

Trials aiming to prove the superiority of a new product without a placebo group are considered justified if the extent of the response of the control product compared with the placebo is great and proven without doubt (Khan et al. 2001). The same prerequisite applies to trials aiming to prove that there is no difference in efficacy between the new drug and the drug currently in use. The use of a placebo is upheld by a situation where there is a minor difference in efficacy between the different therapies, by the inaccuracy of the measuring method available, the variations in severity from one day to another, and also by the desire to obtain the results of the comparison within a short time period and using as few patients as possible (Emmanuel and Miller 2001, International Ethical Guidelines 2002).

The equal efficacy of two products has also been reviewed by comparing the response achieved with a placebo group in previous trials. The use of control groups of the past is not considered necessary, however, because the patient groups in different studies and any other treatments the patients receive usually vary in many respects and the extent of the placebo response also varies from trial to trial (Storosum et al. 1998, Walsh et al. 2002).

The above-mentioned circumstances have resulted in an increase in the number of patients participating in trials, especially during the last decade and more. Inadequate sample sizes are nevertheless still considered a problem in some psychiatric trials (Barbui and Hotopf 2001). In addition to the assessment of efficacy, a placebo group allows the assessment of undesirable effects associated with the drug, because the patients often also exhibit symptoms caused by the disorder under examination or by other illnesses or medical therapies.

## Placebo effect

The placebo response refers to the change in situation of patients in the placebo group during the course of the trial. Even though a placebo is defined as an ineffective treatment pharmacologically, the symptoms of the placebo patients also often vary, for example, during the trial due to the trial arrangements (regularity of the attention paid to the symptoms, and evaluation of their severity) and due to the variable periodicity of symptoms occurring in many psychiatric and somatic disorders (Puustinen and Louhiala 2002). The placebo response is also affected if the trial situation is misinterpreted as a treatment situation. The researcher's own expectations for the efficacy of the treatment may also influence the recovery. The patient's own expectations and desire to please the researcher may increase the placebo response (Cutler et al. 1996).

The prevalence of the placebo response may vary between the different patient groups depending on the duration of the disorder, the subgroup to which it may belong, any concomitant illnesses, genetic background and the number of previous phases of symptoms and the degree of recovery from them. The placebo response may also occur more easily in patients with mild symptoms, and successful randomisation should therefore be especially focused on (Greist et al. 2002).

An extensive placebo response may lead to a situation where the response to the new and the conventional medical treatment is at a level equal to that of the placebo group. Attempts have been made to reduce the placebo response by introducing a short placebo period of approximately 1 week at the start of treatment in all patients to exclude the patients with a placebo response from the trial. This traditional method has not, however, been found to have an effect on the extent of the placebo response (Schatzberg and Kramer 2000). Efforts have been made to assess the extent of the placebo response by studying the emergence of the response, since the placebo response usually emerges quickly and is transient compared with the drug response, which develops more slowly but is of a more permanent nature.

The placebo response in psychosis has been considered to be lower, whereas in anxiety disorders it has been significantly higher. The placebo has been found to decrease the anticipatory anxiety of patients with panic disorder as effectively as an active medication does, but there is a variation in the degree of reduction in the number of panic attacks (Schatzberg and Kramer 2000). Patients with anxiety disorders may be affected by the trial arrangements

more than others, and faced with the fear of social situations the conditioning associated with appointments may decrease the symptoms. On the one hand, however, in severe obsessive-compulsive disorders the placebo response has been sparse, and on the other hand the efficacy of antidepressant therapies given in several studies on antidepressants has not differed from that of the placebo. The placebo response is therefore not categorically associated with the severity of the disorder. An account of the prevalence of placebo response in some psychiatric disorders is given in Table.

***The frequency of placebo response after different metaanalysis***
*(Storosum et al. 1998, Cutler et al. 1996, Schatzberg och Kramer 2000, Keck et al. 2000a, Keck et al. 2000b)*

| *Disorder* | *Frequency of placebo response* |
|---|---|
| *- manic phase in bipolar disorder* | *11–43 %* |
| *- depressive phase in bipolar disorder* | *13–38 %* |
| *- severe depression* | *23–70 %* |
| *- schizophrenia* | *6–43 %* |
| *- panic syndrome* | *ca. 50 %* |
| *- social fobia* | *7–43 %* |

## Potential risks associated with the use of a placebo

The practice of using patient groups receiving a placebo product has been criticised from the ethical and clinico-methodological viewpoint. It has been suggested that the inclusion in a placebo group would be associated with significant risks to the patient's health. In about one in every three studies on antidepressants it has not been possible to point out the difference between the placebo and a control preparation previously found to be an effective antidepressant agent. It has consequently been suggested that placebo-controlled clinical drug trials actually have limited possibilities for producing new information (Mattocs and Horwitz 2001). The investigations also show that the effects associated with trial arrangements may be effective even without the medication.

Psychiatric disorders are known to be associated with the increased risk of suicide (Kasper et al. 1996, Harris and Barraclough 1998). One of the key arguments against placebo-controlled drug trials brought forward in discussions on the ethics of using placebo has in fact been that the inclusion in a placebo group increases the risk of suicide in the patients. The risk has in recent years been reviewed in patients participating in drug trials relative to schizophrenia and severe depression. In the meta-analysis of patients of the placebo group based on a schizophrenia survey by Storosum and coworkers (Storosum et al. 2003), only one patient committed suicide, and according to the researchers' results there was no difference in the risk of suicide between the placebo group and the group receiving the active medical treatment. A meta-analysis of antipsychotic drug trials carried out with four different molecules (quetiapine, clozapine, olanzapine and risperidone) and submitted to the US drug authorities during 1987–1997 arrived at the same conclusion (Khan et al. 2001).

Similar observations have been made in studies on severe depression (Khan and Warner 2000). A meta-analysis of seven different antidepressants, based on the experiences of nearly 20,000 patients participating in the analysis, related to an equal number of suicide attempts and suicides in both the active control or trial drug group and the placebo group. In a later survey carried out with a higher number of patients, the suicidal behaviour of patients participating in antidepressant drug trials did not differ from that of other patients suffering from severe depression (Khan et al. 2003). Based on the above results, it could be judged that patients with increased risk of suicide can, under present trial arrangements, be excluded from the trials. Nevertheless, meta-analyses contain factors of uncertainty, and even though the exclusion criteria appear to work in this respect, any suicidal thoughts or risk of suicidal behaviour of the patients are very closely monitored during the trials (Suokas and Suominen 2002).

Another argument against trials containing a placebo group has been that the patient's disorder is complicated by the absence of the active medical treatment. Drug trials relative to psychiatric disorders are usually of a short duration, lasting for 6-8 weeks on average, which does not delay the start of the treatment significantly (Quitkin 1999). The researcher may also withdraw the patient from the trial if the patient's condition or safety of treatment so requires. Antipsychotic therapy is always only a part of the treatment of psychiatric disorders and some of them can be successfully treated even without any drugs.

## Conclusion

Placebo-controlled clinical drug trials are still considered admissible provided that the survey design is scientifically motivated. In a good survey design the variables affecting the result and the exclusion criteria have been carefully chosen and consideration given to the statistical aspects. The information on the efficacy of drug products given by the meta-analyses widely in use nowadays is more accurate than before and makes it possible to judge more accurately the required size of the trial groups. In addition to the method of using direct placebo-control, an increasing number of other survey frames are used nowadays and will be used in future where the method of placebo-control is combined with another form of analysis. This would, for example, allow patients randomised to a placebo group but unable to benefit from the treatment to be later randomised to other treatment groups.

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**Leila Mälkönen**
SYSTEMEXPERT
National Agency for Medicines

# Accurate information on the availability of drugs

The National Agency for Medicines in Finland has been following the market availability of the actual medicinal products since the mid-1980s, and with the help of the present marketing authorisation data the packages have been under scrutiny since 1997. Information about the availability of drugs on the market was supplemented in the summer of 2004 by comparing the information in the marketing authorisation data base with the information in the drug sales register.

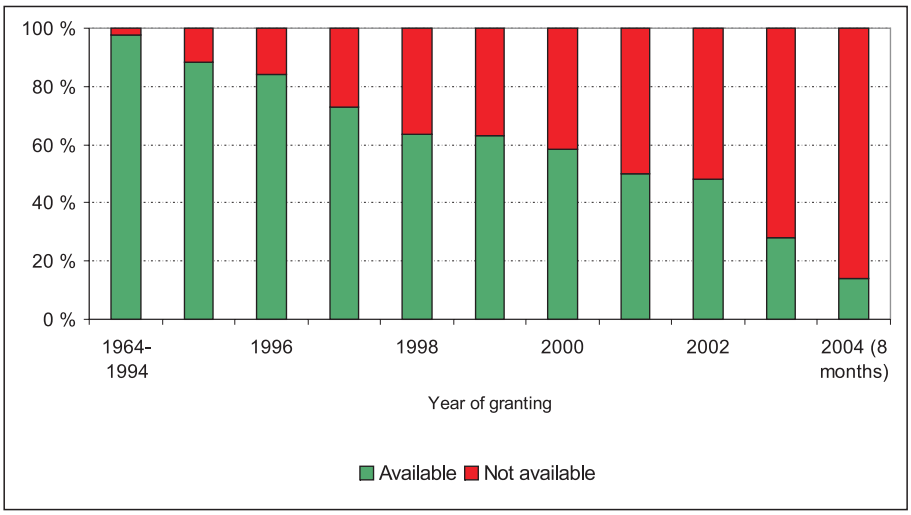


***Fig. 1. The availability of medicinal products by the year when the authorisation was granted***

During this autumn the NAM will introduce a free service on its website, where publicly available information on both human and veterinary drugs can be searched for (www.nam.fi/ ). The service will cover both drugs with currently valid marketing authorisations and drugs with cancelled authorisations and which have been withdrawn from the market. The service will also provide information on whether a certain drug with a marketing authorisation is for sale or not. It is therefore necessary that the marketing authorisation holders inform the National Agency for Medicines of the introduction on to the market of their drugs.

According to the marketing authorisation data system maintained by the Agency, about a third of the medicinal products with valid marketing authorisation are not available on the market. The more recent the authorisation is, the more likely it is that it has not yet been introduced on to the market (Fig. 1). The number of valid marketing authorisations with the authorisation granted three years ago (see p. 52 Editorial) is about 4,170. About 700 of these medicinal products (about 17%) are not on the market in Finland. About 15–20% of these 700 products may have been available on the market earlier, but the packages are not available at present.

These 3-year-old marketing authorisations (4,170 of them) are divided into categories according to the marketing authorisation process as shown (Fig. 2). Of the medicinal products authorised via the centralised procedure only 48% have been introduced on to the market in Finland, and of those authorised via the mutual recognition procedure, in which Finland is the reference member state, only 46% are on the market. In comparison, 94% of medicinal products authorised via the national procedure are available on the market in Finland.

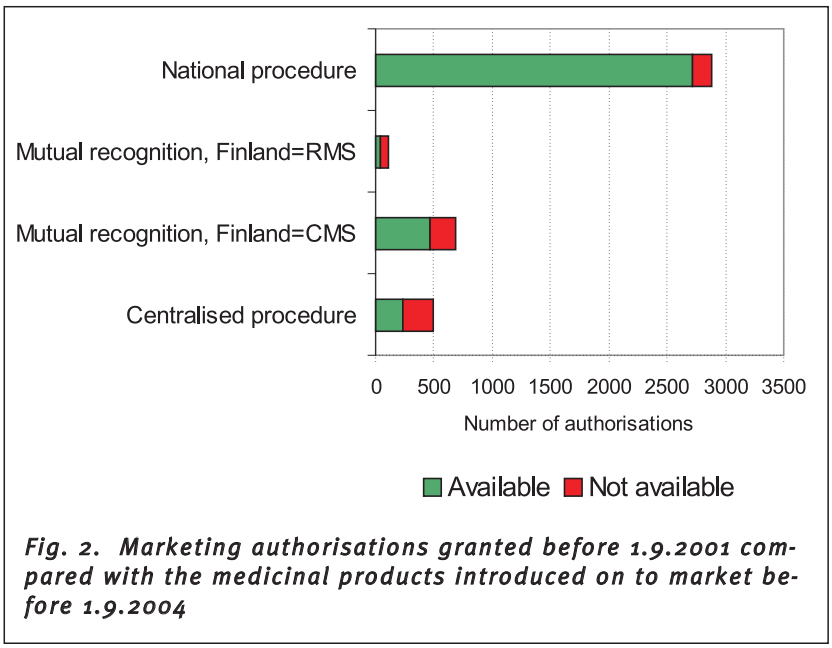


***Fig. 2. Marketing authorisations granted before 1.9.2001 compared with the medicinal products introduced on to market before 1.9.2004***

**Translation Mervi Moisander**