Drug Information Journal, Vol. 33, pp. 627–634, 1999
Printed in the USA.
0092-8615/99

CLINICAL RESEARCH AFTER DRUG APPROVAL: WHAT IS NEEDED AND WHAT IS NOT

GENEVIEVE DECOSTER
F. Hoffmann-La Roche Ltd, Basel, Switzerland
MARC BUYSE
International Institute for Drug Development, Brussels, Belgium

This paper delineates the purposes of clinical studies performed with marketed drugs, often called "Phase IV" or "postregistration" trials. The purposes of these trials are outlined, some design issues specific to them are discussed, and the appropriateness of a full implementation of good clinical practice standards in the postregistration setting is questioned.

Key Words: Phase IV studies; Postregistration studies; Clinical trial design; Good clinical practice

INTRODUCTION

PHASE IV CLINICAL STUDIES are usually defined as those performed with drugs that have been granted marketing authorization (1–4). The term "Phase IV" is fairly standard and covers the vast majority of postregistration clinical study programs. Phase IV studies are also referred to as "marketing studies" or "experience studies" to emphasize that they are conducted once the drug is marketed, rather than prior to its approval by the regulatory authorities. Some other terms, such as "seeding trials" (5) or "observational studies" (6), have also been used, but they usually denote efforts made by marketing departments to encourage physicians to prescribe the new drug, rather than proper trials which are the focus of this paper. Phase IV studies are sometimes confused with postmarketing surveillance, the process of monitoring the safety of a marketed drug (7,8). Phase IV studies are, in fact, part of this process, but their objectives include efficacy or effectiveness in addition to safety (9,10).

The distinction between Phase III and Phase IV studies is not always clear-cut. Many cooperative groups performing clinical trials in cardiovascular disease, cancer, or AIDS call their comparative studies "Phase III" trials regardless of regulatory approval. Seriously compromised patients (eg, with AIDS or advanced cancer) can sometimes get access to a product prior to its approval through "expanded access," "compassionate need," or "treatment IND" programs and in some European countries through special license sales authorized by the health authorities. It has been argued that these programs should be an opportunity to perform large-scale clinical studies addressing a question of scientific interest (11). Such studies, even though they take place *before* the approval

Reprint address: Marc Buyse, ScD, International Institute for Drug Development (ID^2), 430 avenue Louise, 1050 Brussels, Belgium.

of the new drug, would share many characteristics with Phase IV studies. In these situations of life-threatening diseases, new drugs may also go through an "accelerated approval" process in which the new drug is marketed based on limited data and conditional on further evidence being provided in well-controlled studies (12). These subsequent studies, even though they take place *after* the approval of the new drug, would share many characteristics with preregistration clinical trials.

The remainder of this paper will consider Phase IV studies which are conducted with marketed drugs in the indication for which these drugs were approved. Clinical trials testing new claims such as new indications, new routes of administration, or new formulations, are subject to the same requirements as preregistration trials (in the United States, they must be conducted under an investigational new drug application, or IND) and share the characteristics of Phase III clinical trials; such trials will not be discussed further here. This paper delineates the purposes of Phase IV studies, considers some of the design issues specific to these studies, and questions the appropriateness of a full implementation of good clinical practice (GCP) standards in the postregistration setting.

PURPOSES

Broadly speaking, the role of Phase IV clinical trials is to extend knowledge about drug efficacy, and to confirm the safety of a new drug in a wider patient population treated in regular medical care after the drug has been approved for marketing (13).

Effectiveness

While the efficacy of the drug has been demonstrated in a restricted patient population in Phase I–III clinical trials, its effectiveness in a wider population is still largely unknown when the drug comes to the market (14). Table 1 briefly contrasts the notions of activity, efficacy, effectiveness, and efficiency of a new drug.

Phase III clinical trials performed for regulatory purposes usually include highly selected patients, and the results obtained do not automatically translate to the population at large. Phase IV clinical studies, in contrast, include broader patient populations which more closely reflect the reality of medical practice. A case in point is the elderly population, which has historically tended to be excluded from preregistration clinical trial programs and yet account for a substantial proportion of the consumption of medicines.

A second purpose of Phase IV studies is to investigate the relative merit of a newly marketed drug as compared to other available treatments. As indicated in Table 1, the role of Phase I–III trials is to demonstrate that the drug has biological activity and clinical efficacy, hence, the need to compare it, to the extent possible, to a placebo or an untreated control group. In contrast, the role of Phase IV studies is to demonstrate that the drug is effective, hence, the need to compare it to alternative treatments for the disease under consideration.

A third purpose of Phase IV studies is to focus on hypotheses and questions which could not be tested and answered in preregistration trials due to the small number of patients and limited time available before filing for marketing authorization. Questions still unanswered at the Phase IV stage can include the following: long-term benefit or harm of the drug, impact of the drug on secondary endpoints, details of drug administration schedules (such as dose fractionations), combinations with other drugs, the effect of concomitant medications or supportive care, and so forth.

Perhaps the more important purpose of Phase IV studies is to introduce a new drug into routine clinical practice (15). The motivation for doing so is not only commercial, it also has a sound scientific and ethical basis. Indeed, valuable drugs may be underused if clinicians are unconvinced of their merit. Some large trials were conducted with drugs that had a well-known efficacy and safety profile with the only purpose of convincing skeptical clinicians to use them. One striking

TABLE 1
The Main Focus of Different Types of Studies

	Main Focus	Type of Studies
Activity	Biological effect of the drug on the target system	Preclinical studies and early clinical trials (Phase I–II)
Efficacy	Clinical effect of the drug in a sample of well-defined patients	Clinical trials (Phase II–III)
Effectiveness	Overall effect of the drug in a population at large	Late clinical trials (Phase IV)
Efficiency	Balance of costs and effects of the drug from a public health perspective	Pharmacoeconomic studies

example of this situation was a large study of streptokinase and aspirin in the treatment of acute myocardial infarction (16), which was conducted after evidence of the benefit of streptokinase was available from a meta-analysis of several earlier studies (17) as well as from another large trial (18). In spite of the available evidence, streptokinase was not routinely used and was even considered dangerous by some opinion leaders (19). In fact, this situation is common, as is the opposite situation in which an ineffective or potentially harmful drug continues to be recommended by clinical experts (20).

Safety

Phase I–III clinical trials provide preliminary evidence, rather than proof, of the safety of a drug. Phase IV studies provide the ideal setting to further document the safety of a newly marketed drug (9). Because they are properly controlled and closely watched, such studies yield a more reliable safety profile than any method of spontaneous reporting of adverse drug reactions (ADRs), such as yellow cards, case reports, literature screening, and so forth. In particular, the denominator is known in a prospective trial and therefore, the true incidence of ADRs can be estimated accurately. This is especially useful to study *unpredictable* ADRs. Phase IV trials should aim at the detection of unpredictable ADRs and should not focus on predictable, nonserious adverse events or abnormal laboratory data that are not clinically important, since these add no value to what is already known from the pharmacology of the product and from preregistration trials.

While relatively common adverse events are well documented at the end of Phases I–IV, *rare* ADRs will require the treatment of a larger number of patients to be detected. A simple rule is that, if N patients have been treated and no occurrence of a certain event has been observed, then the incidence of that event is less than $3/N$ with 95% probability (21). Thus, at least 10000 patients must be treated for an incidence of 3/10000 to be excluded with reasonable confidence. This number of patients is almost never available at the time of granting marketing authorization to a new drug, and seldom even after Phase IV studies. This justifies long-term pharmacovigilance studies aimed at monitoring drug safety. Such studies clearly extend beyond Phase IV studies and will not be discussed further in the present paper.

DESIGN CONSIDERATIONS

Randomization

The most crucial aspect of Phase IV trials is that they should be based on a sound statistical design (22,23). Claims of effectiveness and/or efficiency can rarely be made on the basis of nonrandomized studies (24,25). Properly randomized studies of sufficient size yield a reliable and definitive answer,

even if they are ultra-simple (26). Publication of their results may have a major impact on medical practice (27). Nonrandomized studies such as "questionnaires" rarely yield a reliable answer, even if they are ultra-complex (28), yet in practice, a large number of nonrandomized Phase IV studies are mounted with the only purpose of allowing clinicians to "gain experience with the drug." The vast majority of these so-called "trials" never get published, which is hardly surprising in view of their vacuity. Mounting nonrandomized Phase IV studies which never get published is scientifically useless and ethically unacceptable.

Large Numbers

One objective of Phase IV studies is to study the effectiveness of a drug in current clinical practice. This implies that the number of patients entered in such studies be large enough so as to answer the questions of interest with reasonable certainty (29). In fact, the efficacy of a new drug may be expected to be lower in Phase IV studies than in Phase III trials, because less responsive patients may be included in the trial, the conditions in which the patients are treated may be less tightly controlled, less experienced clinical investigators may be involved, and so on. The sample size of a Phase IV study should take all these factors into account.

Often the number of patients which would be needed to answer the question of interest is not easily available in a given country, with a manageable number of investigators, or within the budgetary constraints of the marketing department concerned. Such situations may call for a simplification of the study details, but they should never justify the choice of a suboptimal study design. A small randomized study is preferable to a nonrandomized one, or to no study at all! Meta-analysis can be used to combine the results of multiple studies which are individually too small to answer the question of interest. Sometimes a large-scale study is difficult to implement for practical (as opposed to scientific) reasons; in that case, the best option may be to perform several small-scale studies addressing the same question, and to plan a *prospective* meta-analysis of these studies.

Broad Eligibility Criteria

One of the main objectives of Phase IV studies is to study the drug in wide patient populations. This implies that the eligibility criteria in such studies be relaxed as compared to those of preregistration trials. Several authors have discussed the relative merits of strict versus broad eligibility criteria (30,31). As a general rule, strict criteria seem appropriate for preregistration clinical trials, and broad criteria for Phase IV studies. No patients should be excluded from Phase IV studies except if there is a safety concern about their receiving the drug, of if there is a sound basis for targeting the study at a certain subpopulation of patients. The decision to enter a patient in Phase IV study is best left to the discretion of the attending physician, rather than regulated by lengthy lists of inclusion and exclusion criteria. In the limit, the only "eligibility" criteria required is that the clinician be *uncertain* that a patient will benefit from either of the treatments tested (32).

Active Control and Equivalence Trials

Many new drugs have to be compared to placebo to be granted marketing authorization even though an active treatment is known for the disease considered (33). Yet, the relevant medical question is not to show that the drug is biologically active as compared to placebo, but rather to prove that the drug has medical or economical benefits over the currently available treatment(s). Thus, there is an important place for Phase IV studies with "active controls," which are not required for regulatory reasons yet are essential for medical practice (34).

When studies use an active control group, it is often of interest to show that the new drug has the same efficacy as the con-

trol group (rather than higher efficacy), in which case these studies are called "equivalence" studies (or "active control equivalence" studies). Such trials are needed when a new drug is not expected to have better efficacy than the standard therapy, but offers a better safety profile, is more practicable, or is less expensive than the standard therapy, and should, therefore, be substituted for it in routine clinical practice. There is also an important place for Phase IV "equivalence" trials with such new drugs (35).

GOOD CLINICAL PRACTICE (GCP)

GCP Standards

Worldwide acceptance of clinical data demands harmonization in the conduct of clinical trials, thereby allowing patients to have safer and faster access to effective medicines. The main purpose of good clinical practice is to protect the rights, integrity, and confidentiality of subjects participating in clinical research (36). Good clinical practice is also a set of standards defining the responsibilities of the investigator and of the sponsor during the clinical trial process.

Over the past 10 years, GCP standards have been developed (3,36) and sometimes legally enforced (1,2,4) in countries participating in the International Conference on Harmonization (ICH). Other countries (Australia, Canada, Poland, and South Africa) are currently implementing ICH-GCP guidelines in their clinical trial programs.

Slightly different versions of the ICH-GCP guidelines were developed in the three ICH regions (the United States, Japan, and the European Union) (37). Although the legal status of GCP differs in each region, these guidelines should only be followed when clinical trial data are generated for regulatory authority submission (1,4,36). ICH-GCP, however, is becoming the standard applied by the vast majority of pharmaceutical companies for their Phase I–IV clinical trial programs, without distinction of phase or purpose of the trials.

Regulatory Versus Public Health Needs

The evidence which is presented to support the claims of efficacy and safety of new drugs is far more reliable today than ever before, and the cost of ensuring strict adherence to GCP standards is amply justified for regulatory trials. It is not at all clear, however, that such cost is necessary, nor even desirable, for trials performed with marketed products. There is no reason why Phase IV trials should be more strictly regulated than those with over-the-counter drugs, or nondrug trials of surgery, radiotherapy, and other therapeutic interventions. Postregistration clinical studies should reflect the routine administration of treatments rather than experimental situations. In fact, a sharp distinction should be drawn between trials that are intended for regulatory purposes, and those that are intended for public health (38). Jefferys (39) rightly pointed out that GCP requirements should more appropriately be called GCRP, for good clinical regulatory practice.

Many GCP requirements are undoubtedly justified in *all* situations, especially those covering the ethical review of the clinical trial package by an adequate ethics committee or institutional review board, and the patients' consent for their participation in the trial. The uncritical enforcement of the same GCP requirements for postregistration as for preregistration clinical trials may prove damaging, however, because many of the detailed quality control procedures required by the preregistration standards are far away from routine medical practice and are of doubtful or marginal utility.

Simplified Standards

The spirit of GCP can be maintained even if its implementation is adapted to the postregistration setting. First, the intensive monitoring and site visit frequencies recommended by the GCP guidelines fall far beyond the budget of most postregistration programs. Monitoring is among the most costly aspects of trial management, and if

it is required to validate data submitted to regulatory agencies, it may not be needed for studies to yield informative answers. If intensive monitoring is imposed on all trials, a well-intended sponsor might be tempted to reduce the number of patients required by a Phase IV project (or perhaps to drop the project altogether) rather than to relax the GCP requirements so as to keep the budget within reasonable limits. In Phase IV studies, monitoring could well be limited to an initiation and close out visit, or even in some cases to no visit at all. Several large-scale simple studies of thrombolytic therapy after acute myocardial infarction were performed with no monitoring whatsoever (16,18,40).

Second, the collection and filing of essential documents can be considerably reduced in Phase IV clinical trials, as shown in Table 2. Third, quality control, which also needs to be highly detailed in a new drug application, may receive much less attention in the postregistration setting without impairing the scientific validity of the trial (38). For example, checking patient compliance through pill counts would not only be unfeasible, but also pointless in most situations of public health relevance. No measure of compliance is needed when the purpose of the study is to investigate the effect of a drug as actually taken by the patient rather than as intended by the investigator. Since in Phase IV settings the drugs are used as recommended in the summary of the product characteristics, no special safety by the investigator concern should arise from their use.

Finally, some authors, echoing a view which is becoming increasingly fashionable, argue that the *same* standard operating procedures should apply to postregistration studies as to all other phases of research, though they admit that "slight concessions may possibly be made as regards the frequency of monitoring in Phase IV studies" (6). The authors disagree strongly with such a narrow view that makes no distinction between trials of experimental products in their early phases of development and those addressing broader patient management questions.

Discrimination Against Clinical Trials

A very unfortunate (if unintentional) consequence of the insistence that all trials adhere to heavy GCP requirements is that it discriminates against properly controlled clinical trials and encourages other forms of research which yield less reliable evidence.

TABLE 2
Minimum Set of Documents Needed in a Phase IV Trial, and Their Location

	Sponsor	Ethics Committee[1]	Investigator
Protocol and amendments	X	X	X
Case Report Forms (including serious adverse events form)	X	X (blank)	X
Patient information sheets and informed consents	X (blank)	X (blank)	X
Patient source documents			X
Ethics Committee[1] approvals	X		X (local)
Budget	X	X	X (local)
List of participating centers and investigators	X		
Contract Research Organization contracts, if any	X		

[1]and/or Institutional Review Board

For instance, the Working Party on Pharmacovigilance of the European Community (41) identifies various types of study designs that may be appropriate in pharmacovigilance: observational cohort studies, case-control studies, case-surveillance, and clinical studies. The working party stresses the need for clinical studies which do not intrude into routine clinical practice, yet are conducted according to GCP requirements. It follows from the working party's recommendations that an observational (nonrandomized) study is not subject to GCP requirements, whereas a randomized study is. The authors see absolutely no justification for such a discrimination, and fear that it may be counterproductive for future clinical research.

The Public Health Perspective

It is highly doubtful that all clinically relevant questions can or even should be addressed through tightly regulated studies. Regulatory agencies have a mandate to protect patients from potential harm, but they cannot be expected to exert a control over all clinical research worldwide. As a matter of fact, the most urgent public health problems facing developed as well as developing countries need to be addressed through large-scale studies (of vaccines, drugs, or prophylactic measures) for which GCP requirements were not intended, and are ill-adapted. Yet, the GCP guidelines of the WHO, for instance, leave little doubt that *any* trial performed *anywhere* in the word should now fully comply with the *same* set of GCP guidelines:

"Countries in which clinical trials are performed should have regulations by which these studies can be conducted. All parties involved in a clinical trial should comply with the existing national regulation or requirements. In those countries where regulations do not exist or require supplementation, the competent government officials may designate, in part or in whole, the present WHO guidelines for Good Clinical Practice as the basis on which clinical trials will be conducted. . . . Regulatory authorities should have a mandate to revise or terminate trials" (3).

Most investigators would object to the notion that government should be involved at all in revising or stopping a clinical trial! While the WHO recommendations are certainly well intended, they too might benefit from a clear distinction between different phases of research.

CONCLUSION

Blind adherence to GCP standards does not automatically confer validity to a clinical trial. Good clinical practice requirements are primarily aimed at allowing regulatory authorities to check that claims of treatment efficacy are justified; they do not guarantee that the design of the studies is sound, that the question addressed is medically important, or that the answer is relevant in clinical practice. The existing GCP requirements are too fastidious in routine medical care; their uncritical adoption in Phase IV trials may be counterproductive. Phase IV trials must aim at confirming the clinical benefit of a new product in a wide patient population and this is best achieved through large, simple, randomized clinical studies with realistic rather than exhaustive quality control. In the authors' view, GCP requirements should make a distinction between trials aimed at registration of a new drug, and those aimed at the comparison of various patient management policies.

Acknowledgment—This paper updates an earlier version entitled "Phase IV clinical trials: purposes, design, and a limited place for good clinical practice" (*Drug Information Journal*. 1995;29:79–85).

REFERENCES

1. CPMP/ICH/135/95. European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation Units. Effective January 17, 1997.
2. Japan's New GCP and other Rules on Clinical Trials. *Japanese Technical Requirements for New Drug Registration 1997*. Yakuji Nippo, Ltd.; 1997.
3. WHO guidelines for good clinical practice (GCP) for trials on pharmaceutical products. Geneva: World Health Organization; Feb 1, 1994.
4. 21 CFR (Code of Federal Regulations) parts 50, 56,

312, 214, National Archives and Records Administration. Revised as of April 1, 1997.
5. Spilker B. Marketing studies. *Drug News Perspect.* 1990;3(6):369–371.
6. Witte PU. Postmarketing observational studies and phase IV trials in Germany. *Appl Clin Trials*. 1993; 2(7):54–60.
7. Venulet J. Potential role of postmarketing research. *Drug Exptl Clin Res*. 1987;XIII:673–683.
8. Toscani MR, Resnick G. Postmarketing studies: methods for implementation and potential use of data. *Drug Inf J*. 1992;26:261–265.
9. Bell RL, O'Brian Smith E. Clinical trial in postmarketing surveillance of drugs. *Contr Clin Trials*. 1982;3:61–68.
10. Edlavitch SA. Postmarketing surveillance methodologies. *Drug Intel Clin Pharm*. 1988;22:68–78.
11. Ellenberg SS, Finkelstein DM, Schoenfeld DA. Statistical issues arising in AIDS clinical trials. *J Am Stat Assoc*. 1992;87:562–569.
12. Cocchetto DM, Jones DR. Faster access to drugs for serious or life-threatening illnesses through use of the accelerated approval regulation in the United States. *Drug Inf J*. 1998;32:27–35.
13. Hakkaraien H, Hattab JR, Venulet J. Phase IV research by pharmaceutical companies. *Pharmacopsychiat*. 1984;17:168–176.
14. Ray WA, Griffin MR, Avorn J. Evaluating drugs after their approval for clinical use. *N Engl J Med*. 1993;329:2029–2032.
15. Kass Wenger N. Why community physicians should encourage their patients to participate in randomized clinical trials. *Circulation*. 1978;58:963–964.
16. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet*. 1988;ii:349–360.
17. Yusuf S, Collins R, Peto R, et al. Intravenous and intracoronary fubrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. *Eur Heart J*. 1985;6:556–585.
18. GISSI (Gruppo Italiano per la Studio dela Streptochinasi Nell-Infarcto Miocardico). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet*. 1986;ii:397–401.
19. Royal RM. Ethics and statistics in randomized clinical trials (with discussion). *Stat Sci*. 1991;6:52–88.
20. Antman EM, Lau J, Kupelnick B, et al. A comparison of results of meta-analysis of randomized control trials and recommendations of clinical experts. *JAMA*. 1992;268:240–248.
21. Buyse M, Poplavsky JL. Clinical evaluation of virus safety and inhibitor incidence: statistical considerations. *Blood Coagul Fibrinol*. 1995;6 (Suppl.2): S86–S92.
22. Waldron HA, Cookson RF. Avoiding the pitfalls of sponsored multicentre research in general practice. *Br Med J*. 1993;307:1351–1354.
23. Buyse M. Potential and pitfalls of randomized clinical trials in cancer research. *Cancer Surveys*. 1989; 8:91–105.
24. Strom BL, Miettinen OS, Melmon KL. Postmarketing studies of drug efficacy: when must they be randomized? *Clin Pharmacol Ther*. 1983;34:1–7.
25. Byar DP, Schoenfeld DA, Green SB, et al. Design considerations for AIDS trials. *N Engl J Med*. 1990;323:1343–1348.
26. Tognoni G, Alli C, Avanzini F, et al. Randomised clinical trials in general practice: lessons from a failure. *Br Med J*. 1991;303:969–971.
27. Lamas GA, Pfeffer MA, Hamm P, et al. Do the results of randomized clinical trials of cardiovascular drugs influence medical practice? *N Engl J Med*. 1992;327:241–247.
28. Boissel JP. Impact of randomized clinical trials on medical practice. *Contr Clin Trials*. 1989;4:120S–134S.
29. Peto R, Collins R, Gray R. Large-scale randomized evidence: Large, simple trials and overview of trials. *J Clin Epidemiol*. 1995;48:23–40.
30. Buyse M. The case for loose inclusion criteria in clinical trials. *Acta Chir Belg*. 1990;90:129–131.
31. Yusuf S, Held P, Teo KK, Toretsky ER. Selection of patients for randomized controlled trials: implications of wide or narrow eligibility criteria. *Stat Med*. 1990;9:73–86.
32. Stenning S. The "uncertainty Principle" selection of patients for cancer clinical trials. In: *Introducing new treatments for cancer*. Williams CJ, ed. New York: John Wiley; 1992.
33. Temple R. Government viewpoint of clinical trials of cardiovascular drugs. *Med Clinics N Am*. 1989; 73:495–509.
34. Fleming TR. Treatment evaluation in active control studies. *Cancer Treat Rep*. 1987;71:1061–1065.
35. Makuch RW, Pledger G, Hall DG, et al. Active control equivalence studies. In: *Statistical Issues in Drug Research and Development*. Pearce KE, ed. New York: Marcel Dekker; 1992.
36. ICH Harmonised Tripartite Guideline for Good Clinical Practice. Brookwood Medical Publications; 1996.
37. Brown L. Implementation of ICH GCP. *GCP J*. 1998:5;11–14.
38. Buyse M. Regulatory vs public health requirements in clinical trials. *Drug Inf J*. 1993;27:977–984.
39. Jefferys DB. Good Clinical Practice: EC expectations, education, self-regulation, or imposition? *Drug Inf J*. 1992;26:609–613.
40. ISIS-3 (Second internal study of infarct survival) Collaborative group. ISIS-3: a randomized comparison of streptokinase vs tissue plasminogen activator vs anitreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet*. 1992;339:753–770.
41. CPMP Working Party on Pharmacovigilance. Draft guideline for marketing authorization holders on company-sponsored post-marketing safety studies. III/3176/93, 1993.