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# Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization

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**What is already known about this subject**

- The assessment of the added therapeutic value of new medicines with a new active substance is hampered by the lack of appropriate comparative information.
- Though the extent of this information gap is generally perceived as substantial, it has not been quantified.

**What this study adds**

- Information from active controlled trials was available in less than half of the new medicines studied, constituting a significant hurdle for evidence-based decisionmaking on the use of new medicines in initial years following market introduction.

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**Aims**
To investigate the availability of information about premarketing randomized active-control trials (RaCTs) involving medicines with a new active substance at the moment of market authorization in the European Union.

**Methods**
Information was obtained from the EMEA European Public Assessment Reports and the MEDLINE and EMBASE databases.

**Results**
Between 1999 and 2005, 48% of recently approved medicines ($n = 122$) had been studied in comparison with existing medicines at the moment of market authorization. About one-third of these trials were published and publicly available at that moment.

**Conclusions**
For most new medicines evidence-based assessment of the (added) therapeutic value is not really possible at the moment of market authorization.

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## Introduction

For optimal therapy with a new medicine, especially with a new active substance, it is important to know how the new compound compares with existing medicines [1, 2]. This information is necessary to assess the added therapeutic value. For this purpose the optimal study design would be a randomized controlled trial of the new product with an active medicine already used in clinical practice as control group, a so-called randomized active-control trial (RaCT).

Prescribers and reimbursement authorities, faced with a new medicine at the moment of market introduction, need comparative information in order to make decisions on prescribing or reimbursing. This means that ideally a RaCT should be conducted in the premarketing phase of drug development and published before market entry. The absence of RaCTs is generally regarded as an important problem [3, 4]. However, there is a lack of quantitative information about the extent of this problem.

The aim of this study was to investigate the availability of information about premarketing randomized active-control trials involving medicines with a new active substance at the moment of market authorization via the centralized procedure in the European Union and to determine which characteristics of the new medicine were associated with the availability of a RaCT.

## Methods

### *Source of information*

For information about premarketing trials we used the European Public Assessment Reports (EPAR) as they give a good overview of clinical trials submitted by the industry for market approval and the scientific discussion in the Committee for Medicinal Products for Human Use (CHMP) [5]. We selected products with a new active substance authorized by the European Commission between 1999 and 2005. Diagnostics and vaccines were excluded. New active substances were those substances that had not previously been authorized as a medicinal product in the European Union [6]. We used the initial version of the EPAR which was retrieved from the EMEA website [5] at the moment the product was granted market authorization. From the EPARs, we extracted data about the authorization procedure, therapeutic characteristics (indications, mechanism of action, orphan drug designation, biotechnological product) and the clinical studies conducted. To identify relevant RaCTs, we selected all studies that were labelled in the EPAR as 'main/pivotal active-control studies'. An active-control trial was defined as a trial in which a drug under investigation was compared with a known active drug [7].

### *New mechanism of action*

We defined a mechanism of action as new if the primary pharmacodynamic target (e.g. receptor, enzyme, ion channel or carrier molecule) and drug–target interaction differed from existing drugs [8]. When a medicine belonged to a new therapeutic class and the mechanism of action was unknown, we classified it as 'new'.

### *Literature search*

MEDLINE and EMBASE databases using the drug's international nonproprietary name up until the first month after market authorization (actual search date: March 2006) were searched in order to identify which studies reported in the EPAR had been published. We retrieved the abstracts of RaCTs with the new drug and compared the study characteristics and outcomes of the published RaCTs with those reported in the EPAR. Meta-analyses were considered as a publication of a trial when not separately published.

### *Statistical analysis*

In order to assess the association between drug characteristics and the availability of a RaCT, odds ratios with 95% confidence intervals were calculated using logistic regression analysis.

## Results

We identified 122 medicines with a new active substance in the period 1999–2005. For 58 (48%), the initial EPAR reported one or more RaCTs. Table 1 gives an overview of these new substances and Table 2 shows the associations between drug characteristics and the availability of a RaCT. A new mechanism of action was shown to be a significant limiting factor in providing RaCT data (OR 5.11, 95% CI 2.35, 11.13). There was no lack of RaCT data for medicines for the treatment of HIV-1 infections (OR 0.09, 95% CI 0.01, 0.71). No significant association was found for the other main indications and biotechnological products; statistical analysis was not possible for antidiabetic drugs and orphan drugs due to zero values. All the orphan drugs had a new mechanism of action; when these were excluded from a stratified analysis, we still found an association between a new mechanism of action and the availability of a RaCT (OR 3.37, 95% CI 1.50, 7.56).

In total 153 RaCTs were conducted in the premarketing period and mentioned in the EPAR. At the moment of market authorization, we found that 53 trials (35%) of 33 new medicines (27%) had been published.

## Discussion

New medicines are studied extensively in the premarketing phase, but paradoxically enough, there are still

**Table 1**
Randomized active-control trials of new active substances in EU (1999–2005)

1. *New medicines with premarketing RaCT*

a. **New mechanism of action**
aripiprazole, atosiban, bevacizumab (1), cetrorelix, darifenacin, enfuvirtide, fondaparinux, fulvestrant, ibritumomab tiuxetan (1), ivabradine, leflunomide, rasburicase (1), rosiglitazone, sirolimus, trastuzumab (1)

b. **Similar mechanism of action**
abacavir, amprenavir, atazanavir, bimatoprost, bivalirudin, brinzolamide, capecitabine, choriogonadotropin alpha (1), darbepoetin alpha (1), deferiprone, efavirenz, emedastine, emtricitabine, epoetin delta (1), ertapenem, fosamprenavir, ganirelix, insulin aspart (1), insulin detemir (1), insulin glargine (1), insulin glulisine (1), interferon alfacon-1 (1), lopinavir, nateglinide, norelgestromin, olopatadine, palonosetron, parecoxib, pegfilgrastim (1), peginterferon alpha-2a (1), peginterferon alpha-2b (1), pioglitazon, rasagiline, sevelamer, telithromycin, temozolomide, tenecteplase (1), tipranavir, travoprost, valdecoxib, voriconazole, zaleplon, zoledronic acid

2. *New medicines without premarketing RaCT*

a. **New mechanism of action**
agalsidase alpha (1,2), agalsidase beta (1,2), alemtuzumab (1), anagrelide (2), anakinra (1), aprepitant, arsenic trioxide (2), becaplermin (1), bexarotene, bortezomib, bosentan (2), carglumic acid (2), caspofungin, cetuximab (1), cinacalcet, efalizumab (1), eflornithine, eptotermin alpha (1), erlotinib, human protein C (1), imatinib (2), infliximab (1), laronidase (1,2), levetiracetam, memantine, miglustat (2), mitotane (2), nitisone (2), nitric oxide, omalizumab (1), palifermin (1), palivizumab (1), pegvisomant (1,2), pregabalin, sodium oxybate (2), sodium phenylbutyrate, strontium ranelate, tasonermin (1), teriparatide (1), ziconotide (2), zonisamide

b. **Similar mechanism of action**
adalimumab (1), adefovir, alitretinoin, botulinum toxin b, calcitonin salmon (1), colesevelam, daclizumab (1), desloratadine, dibotermin alpha (1), drotrecogin alpha (1), duloxetine, eptifibatide, etanercept (1), human fibrinogen/thrombin (1), lutropin alpha (1), moroctocog alpha (1), oseltamivir, posaconazole, tadalafil, temoporfin, tenofovir, vardenafil, verteporfin

*1 = biotechnological product; 2 = orphan drug.*

**Table 2** Availability premarketing randomized active-control trials of new medicines

| Characteristics | Without | RaCT | With | RaCT | Crude odds ratio (95% CI) |
|---|---|---|---|---|---|
| Number of trials | 64 | 52.5% | 58 | 47.5% | |
| Year of authorization | | | | | |
| 1999 | 9 | 14.1% | 10 | 17.2% | 1.00 |
| 2000 | 5 | 7.8% | 10 | 17.2% | 0.56 (0.14, 2.26) |
| 2001 | 13 | 20.3% | 11 | 19.0% | 1.31 (0.39, 4.39) |
| 2002 | 11 | 17.2% | 10 | 17.2% | 1.22 (0.35, 4.26) |
| 2003 | 7 | 10.9% | 3 | 5.2% | 2.59 (0.51, 13.17) |
| 2004 | 11 | 17.2% | 9 | 15.5% | 1.36 (0.39, 4.79) |
| 2005 | 8 | 12.5% | 5 | 4.1% | 1.78 (0.42, 7.47) |
| Therapeutic indication | | | | | |
| Cancer | 10 | 15.6% | 6 | 10.3% | 1.61 (0.54, 4.73) |
| Diabetes mellitus | 0 | | 7 | 12.1% | NA |
| HIV-1 infections | 1 | 1.6% | 9 | 15.5% | 0.09 (0.01, 0.71) |
| Rheumatoid arthritis | 3 | 4.7% | 2 | 3.4% | 1.38 (0.22, 8.55) |
| Orphan drug | 14 | 21.9% | 0 | | NA |
| Biotechnological product | 26 | 40.6% | 16 | 27.6% | 1.80 (0.84, 3.85) |
| New mechanism of action | 41 | 64.1% | 15 | 25.9% | 5.11 (2.35, 11.13) |

important gaps in the knowledge needed to use them optimally after marketing authorization has been granted. Demonstrating efficacy and safety requires placebo-controlled trials, but for any differences with existing medicines, either positive or negative, we have to rely mainly on trial and error, clinical experience and such like. This study shows that 48% of the new medicines had been studied in an active-control trial, but for only 27% were the results published at the moment of authorization.

We conclude that the lack of comparative data on new medicines, apart from the uncertainty about effectiveness and long-term safety, greatly hamper evidence-based assessment of the therapeutic value of these medicines. This constitutes an extra reason to be cautious about using new medicines during the first years following market introduction and about every claim of an added therapeutic value.

The lack of active-control data is understandable in situations where no alternative active drug is available, as is the case with orphan drugs. However, when alternatives are available, the reasons for this lack of information are less clear. Companies may have methodological, economical and strategic reasons for deciding not to conduct a RaCT. For example, to prove clinically relevant differences between two active substances, trials have to be large and long, which brings added development costs. Furthermore, there is a risk that a new product will prove to be no better than an older, and less costly, alternative. The fact that this risk weighs more heavily than the convincing evidence of an adequate RaCT, is revealing.

When a RaCT has been conducted, its value for the assessment of therapeutic value depends of the quality of the trial. As our study only focused on the availability of information we can not fully discuss this issue. Nevertheless, there is one important general finding. Only 35% of all trials were published at the moment of market authorization and thereby freely available to review and to use as a reference for therapeutic decision-making. This means that EPARs are an important additional source of information, as they give insight into conducted trials and can lead to questioning the industry about their plans for publications. Moreover, they provide weighted information about the significance of the published data.

An important subject of discussion is what should happen in the future to fill in the gaps in comparative information assessed in this study. In view of the importance of comparative studies for pharmacoeconomic assessments and other patient outcome assessments, we had expected to see more RaCTs over the years. Our study does not suggest such a trend. However, we anticipate a change in this trend in the near future because the assessment of therapeutic value and cost-effectiveness requires a scientific basis including RaCT data. The present requirements for clinical trials seem to be sufficient for market authorization, but they are definitely not in the context of the wishes and needs of prescribers, formulary committees and reimbursement authorities.

Today's pharmaceutical market-place is under strong economical and regulatory pressure, and many business analysts are questioning whether the current model of pharmaceutical innovation is sustainable [9, 10]. The costs of drug development are not in balance with the output and there is a strong voice for new scientific and regulatory models for making efficacious, safe and affordable drugs available to patients. In all our efforts to reduce costs, we have to make efficient use of current regulatory requirements. When designing clinical studies, companies should anticipate the need for comparative information. The future therefore probably lies not in more but in smarter and better-designed clinical development programs.

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