

Pediatric Clinical Trials in Germany

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Before drugs are administered to children, they should be adequately tested in that population. No one is likely to disagree with this. Most drugs, however, are not labeled for pediatric use.

One survey, which looked at new molecular entities (NMEs) approved from 1991 to 1995, disclosed that 71% of all new drugs were still not labeled for use in children; other reports estimate the fraction as high as 80%.¹ Another survey looked at drugs approved by the European Medicines Evaluation Agency (EMA). Between January 1995 and April 1998, the EMA granted licenses for 45 NMEs. Out of these only 10 were approved for pediatric use (22%), whereas 29 (64%) had the potential to be used by children.²

There are many reasons why so few drugs have pediatric labeling. For example, the pediatric market share is relatively small. Legal and ethical concerns, such as issues of informed consent and placebo control, can be different from those that arise in adult trials. In addition, there are more practical difficulties. Children often dislike blood sampling, enrolling sufficient numbers of subjects may be challenging, and development of acceptable formulations may be difficult.^{1,3,4}

Seeking to understand how drug manufacturers are coping with these obstacles, we surveyed

research-based pharmaceutical companies in Germany.

The pediatric research climate

Intensive discussions about pediatric trials are going on in Europe. The discussions were stimulated by changes in the United States, where the Food and Drug Administration (FDA) has presented a comprehensive overview of pediatric issues, with regular updates on the Web.⁵ The release of an international guidance document titled "Clinical Investigations of Medicinal Products in the Pediatric Population"⁶ by the International Conference on Harmonisation (ICH) has also encouraged discussions in Europe.

A pending resolution on pediatric medicinal products was issued in December 2000 by the European Parliament and the Council of the Health Ministries of the European Union.⁷ Another step was the foundation of a European Network for Drug Investigation in Children (ENDIC).^{3,8} The situation in Germany is similar to that in the rest of Europe. In August 2000, a representative for drugs for children was appointed at the German Ministry of Health.⁹ Of all the drugs approved by the German Federal Institute for Drugs and Medical Devices (BfArM) in 1997 (excluding vaccines), only five possessed pediatric prescribing information.¹⁰

Our survey

In September 2000, we sent a questionnaire about children in clinical trials to the members of

the German Association of Research-Based Pharmaceutical Companies (VFA). At that time, this association contained 35 leading research-based pharmaceutical companies with more than 60 subsidiaries and affiliated companies, employing altogether more than 76,800 people in Germany, of whom more than 14,000 work in the field of research and development. Together they represent more than two-thirds of the German pharmaceutical industry.¹¹ The VFA was chosen based on the assumption that its members, engaged in research-based drug development, would be more likely than other German manufacturers to be conducting pediatric trials.

The questionnaire asked companies about their activities between 1998 and 2000. The reply rate of 80% was surprisingly high for a questionnaire and indicates the importance of this topic. We evaluated all replies for general information, but only those companies that performed clinical trials in children in the given time frame were used for an in-depth analysis.

General information

Analysis of the replies of all respondents yielded some general information about the study and use of drugs in children.

Number of trials. Slightly more than half of the replying companies (60.7%) conducted clinical trials in the pediatric population or engaged a clinical research organization (CRO) to do it. Altogether, these companies per-

German pharmaceutical manufacturers responded to a questionnaire about testing drugs in children. Their responses indicate that pediatric trials are widespread in Germany.

formed 96 studies. Whereas some of them performed just one study, others carried out up to 25 trials, for example in the field of vaccines. Of the companies that had not done any pediatric trials, almost half intended to start trials in the next two years. The same number of companies, which already conducted trials in children, had decided not to investigate this population further in the near future. Therefore, in the next few years, no increase in drug investigations for children is expected in Germany.

Unapproved uses. Of the respondents, 85.7% offer medicines for children. Although this shows that the majority of companies have experience in the development of medicinal products for children, it remains true that most marketed drugs have not been appropriately evaluated in children. The use of some of these drugs is frequently based on the experience of pediatricians in conjunction with the long history of these drugs on the market. Often, their use is not scientifically tested beforehand.^{1,3}

Unapproved uses of drugs fall into two categories. *Unlicensed* means modification of licensed drugs, such as crushing tablets to prepare a suspension. *Off-label* refers to the use of a medicinal product outside its prescribing information—with other dosages, outside the scientifically evaluated age ranges, via a new route of administration, or for another indication or even a stated contraindication.¹² A series of British surveys investigated unlicensed and off-label drug use in different pediatric settings. They found that unlicensed and off-label prescribing were most common in the youngest patients. The incidence in general practice was 10.8%, in pediatric wards it was 25.1%, and in neonatal intensive care units it was up to 64.6%.^{12,13,14}

Of our respondents, 39.3% were aware that one of their products is used off-label. Reported indication areas of existing off-label use

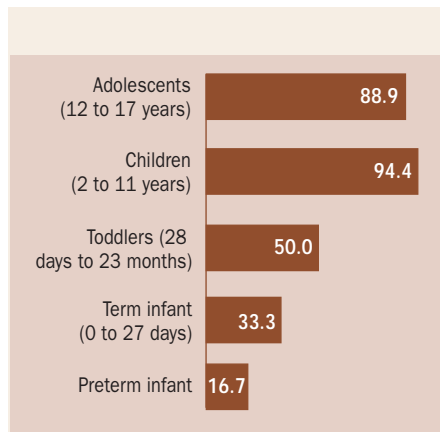


Figure 1. Percentage of companies conducting clinical trials in each age class.

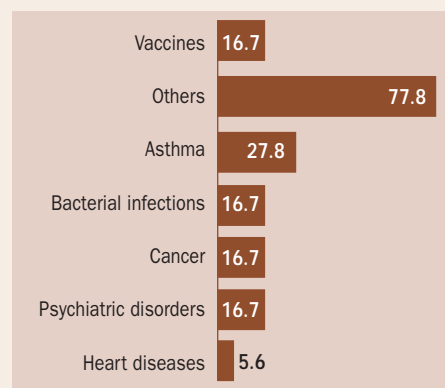


Figure 2. Percentage of companies conducting trials in each indication.

included asthma, cystic fibrosis, depression, epilepsy, gastroenterological disorders, heart diseases, hypertension, juvenile rheumatoid arthritis, migraine, and schizophrenia.

In-depth analysis

Of the responding companies, 18 reported a total of 96 studies conducted between 1998 and 2000 that could be evaluated in detail. We asked respondents to specify investigated indication areas, age ranges, design of clinical trials, number and location of centers, and the participation of CROs. Also of interest was the intended use of trial outcomes, experience regarding recruitment rate, and ethics committee votes. Attempts were even made to obtain opinions about the quality of clinical trials and centers and the difficulties associated with that.

Age groups. We asked companies to indicate the ages of children enrolled in each study, using the categories established in the ICH guidance document E11, Clinical Investigations of Medicinal Products in the Pediatric Population.⁶ As Figure 1 shows, companies were much more likely to have conducted studies in children aged 2 to 17 than in younger children. This distribution reflects the existence of difficulties in conducting clinical trials in the very young. Unfortunately, we did not ask respondents how many clinical

trials they conducted in each age category, nor did we gather the information necessary to correlate age to indication area investigated. It should not be overlooked that a clinical trial can embrace more than one age category.

Indications studied. When we asked respondents to report the indications for which their trials were conducted, we asked companies to choose from six indications that were considered likely to be of interest for investigations in children given for selection, plus “others.” These included asthma, bacterial infections, cancer, heart disease, psychiatric disease, and sera/vaccines. Interestingly, we found out that these were the top six indications reported by U.S. manufacturers in a 2000 survey of pediatric drugs in development conducted by the Pharmaceutical Research and Manufacturers Association (PhRMA).

Surprisingly, few German companies reported having drugs in development for these indications, as Figure 2 shows, although multiple allocations have been allowed. Vaccines are a very specialized field, where only a few companies are active. This could cause the low selection rate in this case. Antibiotics are already available in a vast number of different types, which may be why they were seldom mentioned. Cancer and psychiatric disorders were investi-

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gated only by a few companies. Only one company reported trials in progress for cardiovascular diseases. Asthma and “others” were the most frequently reported indications under study.

When we examined the number of trials per indication area, the distribution changed. Sera/vaccines trials were most numerous, followed by trials devoted to asthma, then a few for psychiatric disorders, bacterial infections, and cancer, with cardiovascular diseases having the fewest trials. Still, a third of all trials were conducted for “other” indications, including allergy, diabetes, epilepsy, growth hormone deficiency, gastroenterological diseases, juvenile rheumatoid arthritis, migraine, skin disorders, transplantation, vascular diseases, and viral infections.

We checked the consistency of the results for asthma against

another source by conducting a literature search covering only the year 2000 and matching the keywords “clinical trials” and “children.” According to this search, 17.5% of the published trials conducted worldwide dealt with asthma, compared with 16.7% in our survey. This could be regarded as an indicator that the German situation is similar to the rest of the world. Unfortunately, the figures cannot be accurately compared to the surveys of PhRMA. While our questionnaire asked about the number of trials enrolling children, PhRMA counted the number of drugs in development for children. In PhRMA’s surveys of 2000 and 1999, 6.5% and 6.3% of all drugs developed for children were for asthma. This may be because the development of a new drug usually needs more than one trial.

Trial design. We asked respondents to describe the design of their trials—randomized, double-blind, or placebo-controlled. All respondents reported conducting randomized studies, two-thirds used double-blind designs, and a similar number used placebo-controlled trials. Because not all companies correlated the number of studies to the kind of trial design, we made an in-depth analysis evaluating only those answers that provided absolute figures. This meant 64 studies could be evaluated. Figure 3 summarizes the results of this analysis.

Study quality. We asked the companies to assess the quality of their own trials. Forty-four percent chose the category “excellent,” 50% “very good,” and 11.1% “adequate.” None selected “bad.” Two firms did not specify the quality of their trials, because all studies were still ongoing. We found it interesting that of the two companies that assessed the quality of their trials as merely adequate, one conducted all its trials by means of CROs.

Use of CROs. Companies reported using CROs in their pediatric trials

to the extent typical in all trials. Most of the companies conducted the pediatric studies on their own (66.7%), some used a CRO sometimes (22.7%), and only a few sourced out all studies (11.1%). In consequence, only 10.2% of all pediatric trials were performed by CROs in the given time period.

Factors contributing to study quality. We asked firms to choose factors that contribute to study quality, giving them a number of factors from which to choose (Figure 4). Although almost all firms assessed good organization by their own company as a prerequisite, their objectivity on this issue might be flawed. Most companies cited collaboration with parents and availability of well-trained investigators as helpful. Next came centers with good facilities, the absence of alternative therapeutic options, and, at the end, high investigator salaries. Additional reasons cited were therapeutic advantages for the child, high interest of investigators, importance of the investigated issue for therapeutic decisions, experienced centers, scientifically based studies of methodologically pure design, and funding of a study assistant at the center.

Number of sites per trial. We wanted to find out whether the mass of pediatric trials was based on a single site, a few sites (two to five), or many sites (more than five). We thought that trials from pharmaceutical companies doing business globally would be internationally conducted, with only a few sites in each country. The results, however, revealed that the majority of the trials were carried out at more than five sites, with some companies reporting an involvement of up to 30 sites. About a quarter of the studies used two to five sites, and only a few of the trials were conducted at one site (Figure 5).

Where were the centers located? Almost half of the studies were conducted at the pediatrician’s office, a third at the hospital,

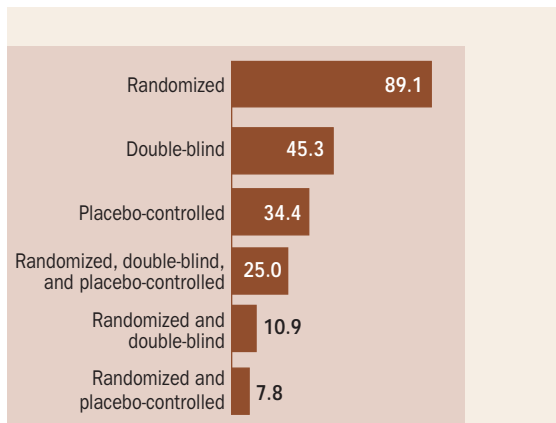


Figure 3. Percentage of studies by trial design.

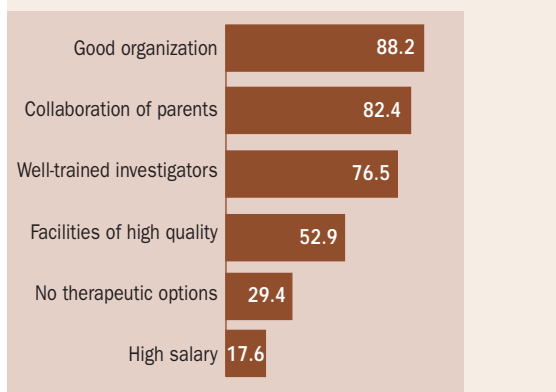


Figure 4. Factors responsible for high-quality trials.

To protect children from the repetition of studies, both positive and negative results should be made available.

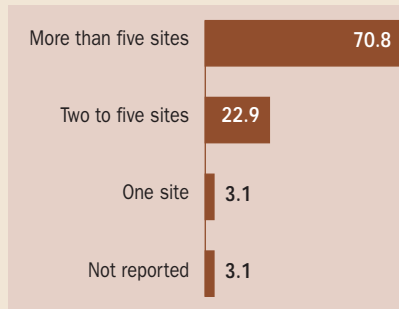


Figure 5. Percentage of companies by sites per trial.

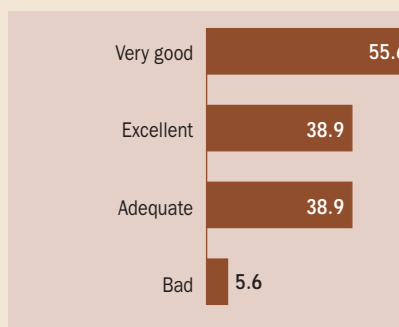


Figure 6. Quality of study sites.

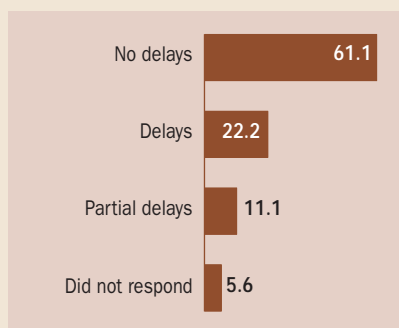


Figure 7. Incidence of delays in IEC approval.

and almost 20%, interestingly, were correlated neither to hospitals nor to general wards. Asked to assess the quality of their investigative sites, companies gave a wide variety of responses (Figure 6).

In interpreting these outcomes, the type of trial, the phase of development, and the disease under investigation should be taken into account. For example, more patients are enrolled in Phase 3 trials than in Phase 2 studies, which of course influences the number of centers. Unfortunately, we did not ask what phase the trials were in.

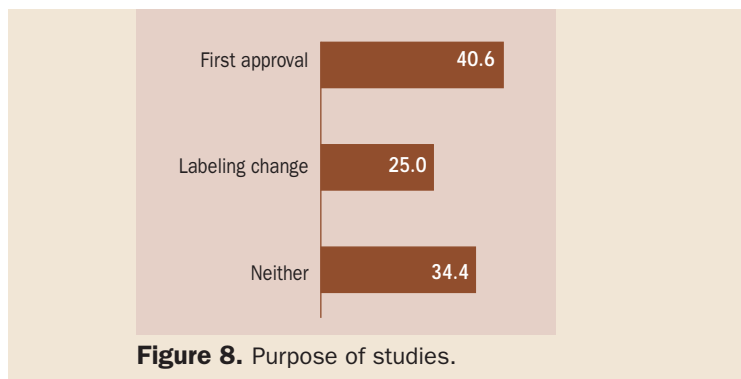
Enrollment problems. We asked companies whether, on average, their sites reached a target recruitment rate of 80% of the planned number of subjects. Less than half of the companies met this target. The remaining companies either reported a clear “no” or made no comment. One reason could be that some trials are still enrolling subjects. Another is that some companies are reluctant to admit that their objectives were not met. For the evaluation it should also be taken into account that in small studies of five to 20 subjects, it may be easier to get a recruitment rate of over 80% than in big trials enrolling hundreds of subjects.

It is not astonishing that 72.2% of the companies admitted to difficulties concerning sufficient enrollment. They mentioned many reasons. Some reasons involved the investigators—they lacked motivation or experience. Another factor was small patient pools, caused either by the incidence of the disease or by badly organized centers. Yet another was the timing of studies in unfavorable seasons. Still other companies mentioned protocol requirements, including visit frequency and too narrow inclusion/exclusion criteria, and difficulties obtaining consent. Interestingly, companies dealing with vaccines or allergies seemed not to be challenged by enrollment difficulties. Perhaps the kind of disease and its prevalence play a role.

Finding investigators. Getting enough qualified investigators seemed not to be a problem for our respondents. About two-thirds reported no difficulty finding sufficient qualified investigators, more than a quarter indicated that they had some problems, and a few made no statement. Investigators’ shortcomings as reported by respondents fell into two categories: lack of theoretical knowledge and lack of practical experience. Shortcomings in the first category were no knowledge of ICH Good Clinical Practice (GCP),⁶ and no understanding of documentation purposes. Shortcomings in the second category included investigators’ tendency to overestimate the size of patient pools. Respondents also complained of investigators’ lack of motivation.

Independent Ethics Committees (IECs). More than 55 different regional IECs exist in Germany. Of these, 19 are located at the medical councils of the federal states, and 36 at the medical universities. Private IECs also exist, but the private ones do not necessarily operate in accordance with the German drug law (AMG), as the others do. Companies reported that IECs hardly ever rejected their pediatric studies. Only one study was rejected, for reasons concerning the age limit. When we asked whether IECs’ decisions were often delayed, almost two-thirds of the respondents reported no delays (Figure 7). The waiting period was “not longer than usual,” as one ironically declared. In Germany, this means two to three months.

Purpose of studies. Last but not least, we asked how companies intended to use the results of the pediatric studies. Publication of results is certainly not the first objective in the conduct of clinical trials, and companies are often accused of publishing only positive trial results and suppressing negative ones. Nevertheless, to prevent duplication of work and



repeated investigations of useless outcomes, and to protect children from the repetition of studies, both positive and negative results should be made available. All but one company responding seemed to be aware of their responsibility and stated a definite intention to publish the results. At the time of the survey only half of the companies had published the results of studies conducted during the period in question. The unpublished results could be for studies not yet completed.

We asked companies why they had undertaken the studies. Surprisingly, companies disclosed that only two-thirds were intended to support a first approval or a labeling change (Figure 8). The rest probably were carried out for marketing purposes or postmarketing surveillance.

A basis for further discussion

This survey demonstrates for the first time the extent of the German pharmaceutical industry’s activity concerning drug investigations in children. It shows that clinical trials in the pediatric population are regularly carried out in Germany. Considering that only 80% of the companies surveyed replied, the number of studies including children might even be higher. The survey showed that the investigated indication areas in the pediatric population are widespread. Factors affecting the quality of pediatric studies included organization by the sponsor, collaboration with parents, and experienced investigators. The requirement for

approval by ethics committees caused no difficulties, but recruitment was a problem for our respondents.

However, this survey also has limitations imposed by the necessity to balance collection of general information for overview and comparison purposes against collection of details to portray reality. It was not possible to consider the uniqueness of every clinical trial. Studies carried out under the main supervision of universities or other parties were beyond the scope of this questionnaire. In consequence, only tendencies can be shown. Nevertheless, the results can provide a solid ground for further discussions and suggestions concerning drug development for children.

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