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A survey of the way pharmacokinetics are reported in published phase I clinical trials, with an emphasis on oncology

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Running title: Reporting PK in phase I clinical trials

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Fig. 1: Flow-chart of the selection process.

ABSTRACT

Objectives: During the drug development process, phase I trials are the first occasion to study the pharmacokinetics (PK) of a drug. They are performed in healthy volunteers, or patients in oncology, and are designed to determine a safe and acceptable dose for the later phases of clinical trials. We performed a bibliographic survey to investigate the way PK is described and reported in phase I clinical trials.

Methods: We performed a MEDLINE search to retrieve the list of papers published between 2005 and 2006 and reporting phase I clinical trials with a PK study. We used a spreadsheet to record general information concerning the study, and specific information regarding the PK, such as the sampling times, number of subjects, and method of analysis.

Results: The search yielded 349 papers, of which 37 were excluded for various reasons. Nearly all the papers in our review concerned cancer studies, although this was not a requirement in the search. Consistent with the selection process, 84% papers explicitly stated PK as an objective of the study.

The methods section usually included a description of the PK (88%), but 10% of the papers provided no information concerning the methods used for the PK, and in 2% the description was only partial. The analysis method was usually basic, with non-compartmental or purely descriptive methods. Observed concentrations and area under the curves were the PK variables most often reported.

The results of the PK study were frequently reported in a separate paragraph of the results section, and only 22% of the studies related the PK findings to other results from the study, such as toxicity or efficacy. In addition, important information such as the number of subjects included in the PK study or the PK sampling scheme was sometimes not reported explicitly.

Conclusion: Concerns about the decreasing cost-effectiveness in the drug development process

prompted the regulatory authorities to recently recommend a better integration of all available information, including in particular PK, in this process. In our review we found that this information was often either missing or incomplete, which hinders that objective. We suggest several improvements to the design and the reporting of methods and results for these studies, to ensure all relevant information has been included. PK findings should also be integrated in the broader perspective of drug development, through the study of their relationship with toxicity and/or efficacy, even in early phase I stages.

Keywords

pharmacokinetics; phase I trials; reporting; survey

1 Introduction

In humans, clinical drug development is initiated with what is termed phase I trials. Phase I trials follow *in vitro* analyses and extensive animal studies designed to select the starting dose for use in humans, i.e., the maximum recommended starting dose (MRSD) [1]. Phase I represents the first translation from basic laboratory work to the clinical setting. Usually, phase I trials are performed in healthy subjects, except when the drug is intended for the treatment of malignancies. Such studies are indeed characterized by the high potential toxicity of assessed drugs at any dose required to be effective and are therefore performed in patients, often patients who have failed several previous lines of treatments. Phase I trials are aimed at obtaining reliable information on a drug's safety, tolerability, pharmacokinetics (PK), and mechanism of action. More specifically, in a healthy volunteer study, the objective is to determine the maximum safe dose under a certain PK or pharmacodynamic (PD) safety limit; for a cancer study, the objective is to determine the maximum tolerated dose (MTD), defined as the highest dose with a relatively low risk of dose-limiting toxicity (DLT), or to recommend a dose level for phase II trials [2].

During phase I, sufficient information about the drug's PK and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, phase II studies [3]. Phase I studies can also be performed in later stages to investigate specific questions, such as the effect of food, modifications encountered in special populations, or drug-drug interactions [4]. Phase I trials therefore often include a PK study. PK studies are intended to define the time-course of drug in the body, and are required in the registration files handed in to the regulatory authority. Furthermore, the determination of dose-exposure-effect relationships is now recognised to be a crucial part of the drug development process [5] and is facilitated by the expanding development of biomarkers and analytical

techniques. Modelling and simulation tools are already extensively and successfully used in many industrial fields outside the pharmaceutical industry, which has shown that PK/PD guided approaches can streamline the development process [6]. The Food and Drug Administration in the US devised a strategy, reported in March 2006 in "The Critical Path Opportunities Report", highlighting specific areas to improve and speeden the development of new, effective and safe medicines [7]. A significant part of that report shows how modelling and simulation techniques can be used to incorporate all the information available from different stages of the clinical development to achieve this goal, using successful attempts at integrated PK/PD development as examples [8].

Over the last decades, many methodological developments have been proposed to analyse data from PK studies. A large part of these relate to the so-called population approaches, where the average parameters and their associated variabilities are estimated through nonlinear mixed-effect models [9], and which are invaluable when the design of the studies is sparse or variable between subjects [10]. Non-compartmental approaches and individual nonlinear regression have also been extended. Many software have been developed to perform these different types of analyses. However, the extent to which these methods are actually applied in clinical trials has not been evaluated.

Our aim in this paper was to evaluate, through a bibliographic survey the way PK studies of phase I clinical trials, how these trials are reported and analysed. More specifically, we were particularly interested in the following points: (i) the description of the PK study; (ii) the methods used to analyse the data; (iii) the completeness of the results reported, (iv) the concordance between presented methodology and reported results, and (v) whether the results are used to bring additional information to the study. It should be noted that the aim of this paper is not to judge the quality of publications, since there is no validated tool for that, but to see if the PK part of a published clinical trials is well reported and can be understood by all readers.

2 Materials and methods

2.1 Article selection

PubMed was used to retrieve the references of all the papers corresponding to the following criteria: "phase I" or "phase 1" in title, pharmacokinetic* anywhere (title, abstract, keywords). The search was limited to 'English language' and to papers published in 2005 and 2006. The full text was then retrieved.

2.2 Data abstraction form and analysis

Our objective was to determine how much information concerning the PK study was reported in the papers describing the phase I study. We built a data abstraction form, which corresponds to a checklist of items [11]. The form was then structured as a spreadsheet with each column representing one item, and the readers filled one line for each paper read. The form was used to extract a large number of informations from the articles and allowed statistical analysis of the results. In addition to items describing the pharmacokinetic study of the trials, we also extracted general information concerning the paper and the trial itself. We now describe in detail the items included in the data abstraction form.

We first included in the spreadsheet a number of items describing the authors of the study: the name and address of the first author, whether a statistician, a pharmacokineticist or a pharmacologist was present amongst the co-authors (based on the affiliations). We also recorded industrial partnership, by checking whether scientists from the pharmaceutical industry were co-authors, and whether the study was sponsored by the pharmaceutical industry, based on the declarations of conflict of interest and of grants received.

The next series of items described the phase I study: the title of the paper, the journal, the year of publication, the main drug tested and whether associated drugs have been tested, the primary and secondary objectives of the study, the patient population (adults or children) and the disease for which they were treated (if any). Since a large portion of phase I clinical trials deal with anticancer drugs, we also recorded whether the tumor response was evaluated when appropriate.

Given that phase I clinical trials are designed to investigate several doses of the drug and to test the tolerability of the drug, the next series of items described the design of the study: the number of subjects included, the planned number of drug levels, the dose-escalation scheme, the total number of dose-limiting toxicities that occurred during the study, whether MTD was reached or not, and whether patient selection was performed before the analysis. If several drugs were included, double-escalation was checked when both drugs under study were escalated, either together or sequentially.

Finally, a number of items specific to the PK analysis were then included in the spreadsheet: the number of subjects included in the PK study, whether the PK sampling scheme was described, whether the PK was sampled on one or more occasions, the dose levels for which PK was sampled, the PK variables reported, and whether the relationships PK-toxicity and/or PK-efficacy were investigated. If several drugs were included, we also recorded whether a PK interaction study was performed. In addition, we recorded the analysis method used to analyse the PK, the software, and whether a model was built to describe the PK.

The first 40 papers were read by both authors who then met to compare the results entered in the data abstraction form and to assess the reproducibility between the two readers. All discordant results were checked and corrected. The next papers were divided equally and read by only one reader.

Once the survey was completed, we used descriptive statistics (median and range) for continuous

variables and frequencies and percentages for categorical variables. Chi-square tests were used to perform stratified analyses with respect to the primary objective of the study. Data management and statistical analyses were performed using R (version 2.4.0) [12].

3 Results

3.1 General results

The flowchart resuming the selection process is given in figure 1. The keyword selection retrieved 354 papers over the two year period considered; of these, 4 appeared twice in the list, and one study was split in two papers, which were regrouped for the analysis. Twenty-four papers were excluded because they did not meet the criteria we set on the search (date of publication, language and study performed in humans). Twelve papers were found not to be drug studies, or not to include phase I data. Finally, one paper was not available from any source we had access to, including direct contact with the author. In the following, we therefore used a database of 312 papers, of which 40 were read by the two authors and the remaining by only one author.

Table I gives the main characteristics of the studies. Industrial partnerships were identified based on co-authorship, financial support, or both in 86 papers (28%). The identification of a statistician or a pharmacokineticist was based solely on the affiliation which was sometimes limited to the university or the pharmaceutical company. As seen from the table, an overwhelming majority of papers published concerned cancer studies. The main objective of the study was exploratory in 139 papers (45%, of which 126 cancer studies), regrouping first-in-man or first-in children studies, new formulations, special population including use of drugs in new pathologies, while it was confirmatory in 173 papers (55%, of which 164 cancer studies), with a majority of these being studies evaluating com-

bination therapies or new administration schedules. We also recorded the specific objectives stated in the paper: in accordance with the selection criteria, the determination of the PK was an objective in 84% of the studies (n=262). Because of the number of cancer studies found in the survey, the determination of the MTD was an objective in 215 studies (69%) and the investigation of toxicities or DLT in 165 papers (53%). The studies were nearly always designed with multiple objectives in mind (in N=279 studies, 89%). We also noted that in a few papers, the objective was not clearly stated in the abstract or the introduction. The number of subjects included in the studies was typically rather low, as expected from phase I studies, but a few studies included over 100 subjects.

Because we only found 22 papers which investigated non-cancer drugs, these tables and the following results will focus only on the 290 studies in the oncology field. We performed stratified analyses on the primary objective. The primary objective did not significantly change the proportion of papers involving a pharmacokineticist or a statistician, nor the proportion of studies performed in collaboration with an industrial. The size of the study however was slightly larger in confirmatory studies (median 32, range 6-105) than in exploratory studies (median 28, range 7-91, $p<0.05$).

3.2 Pharmacokinetic study

Our main focus in this paper was to examine how the PK part of phase I studies was reported. The results concerning the PK study are reported in table II and III. Of the 290 studies in the oncology field, 7 did not include PK, so the two tables report the findings on 283 papers.

In the methods section, the description of the PK section was available in most papers; however, 30 papers did not describe the design of the PK study at all or mentioned only the number of samples, and in 5 the description was insufficient (sometimes describing only partly the sampling schedule or mentioning weekly samples without the timing). Sampling was performed on at least two occasions

in 65% of the studies, but in several papers, although the sampling schedule on the first occasion was described, we could not determine the number of additional samples or their exact timing when reading the paper. Also the number of subjects included in the PK study could not be found in 34 papers (12%) and was not apparent in many others.

Combination therapies were investigated in 120 papers (table III), of which 113 included 2 drugs (94%) and 7 included 3 drugs or more (6%). Combination studies represented 54% (n=51) of the studies performed by academia alone, but only 37% (n=69) of the studies performed with financial support from the pharmaceutical industry ($p<0.007$ according to a χ^2 test). Only 38 studies however included double escalation procedures, where the different drugs are escalated separately: in most cases only the main drug is escalated. Twenty-one of these studies were self-described as PK interaction studies, but in fact 48 studies investigated the interaction between the drugs, although half considered only the effect of one drug on the PK of the other(s).

PK data was most often analysed by non-compartmental methods (NCA), alone or in combination with more advanced approaches (n=14). In 21 papers (7%), the reporting was purely descriptive, showing plots of concentrations versus time or reporting summary statistics of trough or steady-state concentrations. The method of analysis was not reported at all in 50 papers. Modelling, using population approaches or individual estimation, was used in few papers (20% of the total); in one of the papers, a model described the PD of the drug but it was unclear whether the PK had also been modelled. In the 227 papers where the analysis was described and was not descriptive (n=212), the software used for the analysis was quite often not reported (n=37, 17%); when it was reported, the software WinNonLin, which can be used for NCA and RNL analyses, was the most frequently cited (n=119, 56%). As a result of this choice of methodology, the PK variables most often reported were the area under the curve (AUC) as a measure of drug exposure, observed concentrations such as con-

centration profiles,peak (C_{max}), steady-state (C_{ss}, or trough (C_{trough}) concentrations, and parameters obtained through non-compartmental analyses such as the clearance (CL), volume of distribution or half-life.

Extensive sampling was a rule: the median number of samples collected on a single occasion was 10 (range 1, for some studies collecting only steady-state samples in routine therapeutic drug monitoring, to 26), and the total number of samples varied from 2 to 54, with a median of 15; in 30 papers the number of samples was not clearly reported or varied within subjects as the samples were collected during long-term treatment. There was no difference in the number of samples depending on whether the method was NCA or RNL versus population methods. The number of subjects reported in the PK analysis was less than the total number of subjects included in the study in 138 papers. Reasons for excluding data included "patient's will to participate in the PK study", or "concentrations undetectable for low doses", but they were seldom stated explicitly in the paper. PK was investigated usually at several drug levels and in majority at all drug levels studied (n=207 studies), although this information was often deduced from the tables reporting the PK results and not explicitly stated, and sometimes could not be determined (n=24).

Stratified analyses were performed to investigate the differences between papers using basic methods (descriptive or NCA) versus papers using modelling approaches. Papers published by academia alone were slightly more likely to involve modelling (non-linear regression or population methods, 22 out of 76) than papers involving an industrial partner (19 out of 157, $p<0.003$). When modelling approaches were used, there were also slightly less samples taken (median 33 versus 39 for studies using NCA), but this trend was not significant. The same results were obtained when assuming that the papers not reporting the analytical method (n=50) had used basic approaches.

The results of the PK study were usually described in a separate paragraph of the paper, and

in majority no attempt was made to relate the PK results to the toxicity of the drug, or any other result from the study (efficacy, evolution of a biomarker...). In 34 papers an attempt was made at investigating the relationship between PK and toxicity: in 7 papers, this was purely descriptive, in 19 papers, a correlation or regression between a toxicity marker and PK parameters was tested, and in 8 papers a logistic model was used. In 35 papers the relationship between PK and efficacy was studied: in 7 papers this was descriptive, in 22 papers correlation or regression was used to relate the PK with the evolution of a biomarker, while in 6 papers logistic regression or modelling was applied. In 64 papers (22%) both efficacy and toxicity were studied in relationship with PK.

4 Discussion

In this paper we present a survey of the papers reporting phase I studies and including PK. The guidance for PK studies in humans, issued by the FDA, contains a number of recommendations concerning the content of the report to be filed when a new drug application is submitted [4]. These items are considered necessary to judge the validity of an application, and although they cannot all be reported in a scientific article, we used this guidance as a basis to establish the data abstraction form described in the present paper.

We read 312 papers published over 2005 and 2006 and reporting phase I studies with PK. We found an overwhelming majority of the papers in our survey to be published in oncology. This reflects in part a selection bias in our initial Medline search. Indeed, our search included the following criteria; (1) "Phase I" or "Phase 1" in the title of the published paper, (2) "Phamacokinetic" anywhere, (3) paper published between 2005 and 2006, (4) clinical trials as search limit, and (5) English paper as search limit. This Medline search yielded 349 papers in which 37 papers were excluded (review, not

pharmacokinetic study, etc) and 290 (83%) were oncology clinical trials or related to oncology trials. Phase I trials in oncology may be more likely to be identified as such in the title. To check this, a second Medline search was done to estimate the selection bias, in this new search all previous criteria were similar except the first one, which was changed to "Phase I" or "Phase 1" anywhere. 590 papers were found in which, based on title and abstract, 422 (71%) papers were identified as oncology or related to oncology trials, and 67 papers (11%) excluded. Thus, the high percentage of oncology trials found in the present study is slightly overestimated but oncology trials still represent the majority of published phase I trials.

The large majority of papers found in oncology with both the initial and modified search is probably a combination of two factors. The first is a selection bias, in that phase I trials appear more likely to be identified as such in the oncology field where there may be a more standardised approach to these studies. The second is a publication bias due to the way subjects are recruited. Indeed, subjects recruited in phase I studies in oncology are usually treated at the hospital and such studies are performed in collaboration with hospital physicians and researchers, whereas studies in healthy volunteers are mostly performed within the pharmaceutical industry or increasingly outsourced to clinical research centers, and publications are not necessarily encouraged. A possible work-around the publication bias could be to survey Final Study Reports, submitted to and reviewed by Health Authorities. However, these reports are not readily accessible, and existing registries such as www.clinicalstudyresults.org, developed by the pharmaceutical industry to provide greater access to the results of its clinical studies, or www.cancer.gov/clinicaltrials/ct-types-list, include mainly results from later phases in drug development.

An industrial partner was involved either as co-author or through financial support, in two-thirds of the papers surveyed, meaning one-third were purely academia. Support by the pharmaceutical in-

dustry, in the form of a grant or by furnishing the drug under study, was reported in 40% of the papers surveyed; however, it was not always clear in the other 60% whether the drug had been furnished, so this figure may be slightly underestimated. Even so, we expected that most of phase I studies should involve an industrial partner, since these studies are usually initiated by the pharmaceutical industry. Again, this could be related to a publishing bias whereby phase I studies performed in the pharmaceutical industry are not all published.

We also attempted to determine the percentage of studies involving statisticians or pharmacokineticists/pharmacologists, but these items proved tricky to establish. Based on the affiliation reported alone, we found few departments of statistics or biostatistics explicitly stated, and similarly departments of pharmacology or pharmacokinetics were seldom found. It is also possible that, when the papers were published in collaboration with the pharmaceutical industry, the statistical and PK analyses were performed in-house. Although this does not necessarily mean that statisticians or pharmacokineticists were not part of the project, we did note that the PK analysis was usually quite basic.

In the remaining part of the paper, we focus on oncology trials owing to the limited number of papers outside this area.

The PK study was usually described in separate paragraphs, both in the methods and the results section, and rarely related to the other findings in the study such as toxicity. The description of the methods was usually appropriate, except in a few papers where, as pointed out, sampling times were not described. However the description of the results were not as standardised, and information was often missing. This made it more difficult to find the relevant results, especially for non-pharmacokineticists. PK results were also frequently reported separately for the different doses, with no attempt made at providing an overall information which could be extrapolated and used in later

phases of drug development.

Modelling was seldom applied, and in majority PK data was analysed using non-compartmental approaches. When modelling was used, it did not appear to have an influence on the design of the studies. A large number of studies involve measurements on at least two occasions (such as after 2 doses), as per the recommendation of the regulatory authorities on population PK [13], but within subject variability was never investigated even though this may be a key point for future drug administration. Modelling approaches can be useful for decision purposes [3]. PK or PK/PD models developed using the data from phase I studies can be applied to guide dosage decisions for phase II, evaluate alternative formulations or drug delivery systems, or investigate alternative dosage regimen for multiple dose studies [8]. As such, modelling can also play a pivotal role in the drug approval process [14]. Another point to note is that the number of subjects for which the PK was studied was often not reported, and in many papers the number of subjects with PK as reported in tables appeared less than the total number of subjects, while the reason for that was seldom reported. Sometimes the subjects were considered not be evaluable for PK and their data apparently discarded, but modelling approaches could have been used to incorporate all the available data even when NCA methods fail.

In a recent survey performed by the FDA concerning the low rate of success of new drug applications, the department of Pharmacometrics states that "one of the major criticisms against drug development is its negligence to employ prior knowledge to drive drug development decisions such as trial design and analysis", leading to the proposal to improve the process [7]. Integrated PK/PD development has been proposed as a more effective use of knowledge and decision making to be used prospectively during drug development [15, 8]. In the present survey, we found that seldom was any attempt made to relate the PK findings to the other results of the study. In particular, hardly ever was the occurrence of toxicities related to individual PK parameters such as exposure, even though most

of the studies were cancer studies where toxicities are dose-limiting and interindividual variability was usually high. It is of course possible that such a study was performed at another time during the development of the drug, or that it was reported in a separate paper or in the registration file submitted to the regulatory authorities.

In 2001, Margolin et al. performed a detailed review of clinical trials reporting high-dose chemotherapy regimens [16]. As we do in the present survey, they noted the lack of correlative pharmacologic analyses, and suggested guidelines for the design of such trials. Their suggestions included statistical input into the design, execution, analysis, interpretation, and reporting of these studies, as well as more homogeneity in the analysis methods [16]. Recent regulatory recommendations have in addition emphasised the benefits of better integrating all information during the drug development process, explicitly stating PK [7]. Despite these recommendations however, our study shows that there is still room for improvement both in the reporting and in the analysis of the PK studies.

Several factors may explain the relative paucity of usable data we found in this survey. First, the amount of information contained in a phase I clinical trial requires a concise report of the different sections, including PK. However, some informations like the number of samples, the description of the sampling schedule, as well as the reasons why some data was discarded, need to be explicitly stated. In our study, we often had to deduce such information from tables or figures, and sometimes we could not find it. Second, the emphasis of the publication may be more on the clinical findings than on the PK; however, in 84% of the papers we surveyed, the determination of the PK of the drug was explicitly stated as a primary objective and therefore probably deserves a more complete reporting. Third, the editorial process may also contribute to a standardisation of the reporting, however additional material can now often published online. Fourth, PK studies are also published in their own right and more sophisticated modelling may well have been performed after the reporting of the initial study,

justifying a separate publication. However even in this case it is important to provide in the initial report a complete description of the data obtained, including the reasons for which some subjects are not included in the PK analysis.

Quality is a major issue in randomized clinical trials. For instance, the CONSORT (Consolidated Standards of Reporting Trials) statements were developed, encompassing various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of clinical trials. Although it can be argued that all randomized controlled trials are not comparable, the CONSORT Statement developed a 22-item checklist to evaluate how the trial was designed, analyzed, and interpreted. In the same way a similar initiative could be realistic in the context of phase I clinical trials. Recently, Strevel et al. have proposed a quality score to assess the quality of abstract reporting for phase I cancer trials [17]. Similar quality scales or checklists could be developed to assess the reporting of the PK studies in published papers.

5 Recommendations

In order to improve the reporting of PK analyses in this field, we suggest improvements in three main areas: design, reporting of the methods used, and reporting of the results.

First, the design of the PK study should include the study of several, if possible all, doses of the drug; regulatory authorities are particularly interested in examining "the changes in kinetic parameters within the recommended dosing range", and suggest examining when appropriate the influences of demographic characteristics [4]. Although the FDA guideline on human PK in new drug application did not explicitly mention assessing the within-subject variability when it was issued in 1987, a later guideline from the same agency and dealing with population pharmacokinetics devotes a subsection

to the "importance of sampling individuals on more than one occasion" [13], which contributes to the changes in pharmacokinetic parameters. We therefore recommend to evaluate the within-subject variability in pharmacokinetic parameters, as well as the between-subject variability. In the present review, we found that most of the studies we collected administered multiple doses of the drug, which make this recommendation quite feasible, and a large number already followed it. Finally, around half of the papers we reviewed studied a combination of drugs; for these studies, sampling of all drugs should be performed to provide information on individual exposure for each drug.

Second, we recommend that the methods section describe: the number and timing of samples taken; the range of doses; the method used for the analysis of the PK, clearly stating whether modelling was used; the software and the estimation algorithm; if modelling was used, the method for data weighting and the model used for residual error; a motivated choice of the PK parameters of interest; whether PK was related to other findings in the study, and if so, a description of the analysis; for studies with several drugs, whether drug interaction was studied and the method used, as well as whether both drugs were escalated separately and the combined scalation scheme.

Third, the results section should contain the following information: the number of subjects included at each dose level; the number of subjects with PK and the justification for not including certain subjects in the pharmacokinetic analysis, the distribution of the estimated parameters at each dose level; the respective contribution of within and between subject variability for each parameter; a table summarising PK parameters across all doses if the PK was found to be dose-proportional, and PK parameters estimated using an appropriate model if it was not.

In addition to these three key areas, we would like to suggest trying to relate the PK findings to the other results in the study, such as toxicity and/or efficacy. Integration of PK results in the broader picture of drug development is currently lacking [7], as is a less discontinuous development

process, and this has not much progressed since previous reviews [16]. For instance, when biomarkers of the toxicity or the efficacy are measured, modelling can be used to detect a concentration-effect relationship. The relationship of PK parameters of exposure such as the AUC with binary endpoints can be studied using logistic regression; boxplots of measures of exposure versus the endpoint can be plotted and descriptive statistics and correlation tests can be given. In all cases, the information could be tabulated and stored for use in later studies, possibly in Web appendices. Finally, phase I clinical trials often include extensive sampling to describe the entire PK profile, which could be more often modelled to provide a first description of the PK and guide subsequent developments.

6 Conclusion

In conclusion, the present survey showed that there is still progress to be made concerning the reporting and the analysis of the PK part of phase I clinical trials. The impact of the present survey is limited to clinical trials in oncology because of the small number of studies that were not related to cancer drugs. We propose a number of recommendations to improve the reporting of the PK sections of these trials.

References

[1] Reigner B, Blesch K. Estimating the starting dose for entry into humans: principles and practice. Eur J Clin Pharmacol 2002; 57 (12): 835–45

[2] Zhou Y. Choice of designs and doses for early phase trials. Fundam Clin Pharmacol 2004; 18 (3): 373–8

[3] Aarons L, Karlsson MO, Mentré F, et al. Role of modelling and simulation in phase I drug development. Eur J Pharm Sci 2001; 13: 115–22

[4] Food and Drug Administration. Guideline for the format and content of the human pharmacokinetics and bioavailability section of an application. 1987. Available from URL: http://www.fda.gov/CDER/GUIDANCE/old071fn.pdf

[5] Dingemanse J, Appel-Dingemanse S. Integrated pharmacokinetics and pharmacodynamics in drug development. Clin Pharmacokinet 2007; 46: 713–37

[6] Gieschke R, Steimer JL. Pharmacometrics: modelling and simulation tools to improve decision making in clinical drug development. Eur J Drug Metab Pharmacokinet 2000; 25: 49–58

[7] Food and Drug Administration. Innovation or stagnation: critical path opportunities report. Rockville, Maryland, USA, 2006. Available from URL: http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf

[8] Chien J, Friedrich S, Heathman M, et al. Pharmacokinetics/pharmacodynamics and the stages of drug development: Role of modeling and simulation. AAPS J 2005; 7: E544–59

[9] Pillai G, Mentré F, Steimer JL. Non-linear mixed effects modeling - from methodology and software development to driving implementation in drug development science. J Pharmacokinet Pharmacodyn 2005; 32: 161–83

[10] Retout S, Mentré F. Optimization of individual and population designs using Splus. J Pharmacokinet Pharmacodyn 2003; 30: 417–43

[11] Boutron I, Tubach F, Giraudeau B, et al. Methodological differences in clinical trials evaluating nonpharmacological and pharmacological treatments of hip and knee osteoarthritis. JAMA 2003; 290: 1062–70

[12] R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria, 2004. Available from URL: `http://www.R-project.org`

[13] Food and Drug Administration. Guidance for Industry: Population Pharmacokinetics. Rockville, Maryland, USA, 1999. Available from URL: `http://www.fda.gov/cder/guidance/index.htm`

[14] Bhattaram VA, Booth BP, Ramchandani RP, et al. Impact of pharmacometrics on drug approval and labeling decisions: A survey of 42 new drug applications. AAPS J 2005; 7: E503–9

[15] Bruno R, Vivier N, Veyrat-Follet C, et al. Population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships for docetaxel. Invest New Drugs 2001; 19: 163–9

[16] Margolin K, Synold T, Longmate J, et al. Methodologic guidelines for the design of high-dose chemotherapy regimens. Biol Blood Marrow Transplant 2001; 7: 414–32

[17] Strevel EL, Chau NG, Pond GR, et al. Improving the quality of abstract reporting for phase I cancer trials. Clin Cancer Res 2008; 14: 1782–7

Tables

Table I : Characteristics of the 312 papers read in the present study. For the items 'Country', 'Statistician' and 'Industrial' the answer 'no' means 'no' or 'not reported'.

Item		N (%)
Year	2005	171 (55%)
	2006	141 (45%)
Country	North America	186 (60%)
	Europe	90 (29%)
	Asia	27 (9%)
	other	9 (2%)
Statistician	yes	46 (15%)
	no	266 (85%)
Pharmacologist/Pharmacokineticist	yes	81 (26%)
	no	231 (74%)
Industrial partner (*)	co-author	172 (55%)
	support	126 (40%)
	none	100 (32%)
Pathology	cancer	290 (93%)
	infectious disease	7 (2%)
	other	15 (5%)
Age	adults	289 (93%)
	children and adults	4 (1%)
	children/young	19 (6%)
Population	patients	299 (96%)
	healthy volunteers	13 (4%)
Main study objective	first-in-man	79 (25%)
	special population or pathology	35 (11%)
	formulation	18 (6%)
	feasibility	7 (2%)
	combination therapy	105 (34%)
	schedule evaluation	33 (11%)
	PK/PD	18 (6%)
	other	17 (5%)
Number of subjects	median [range]	26 [6-151]

(*) multiple answers possible

Table II : Characteristics of the pharmacokinetic study reported in the 283 papers concerning oncology trials and including PK.

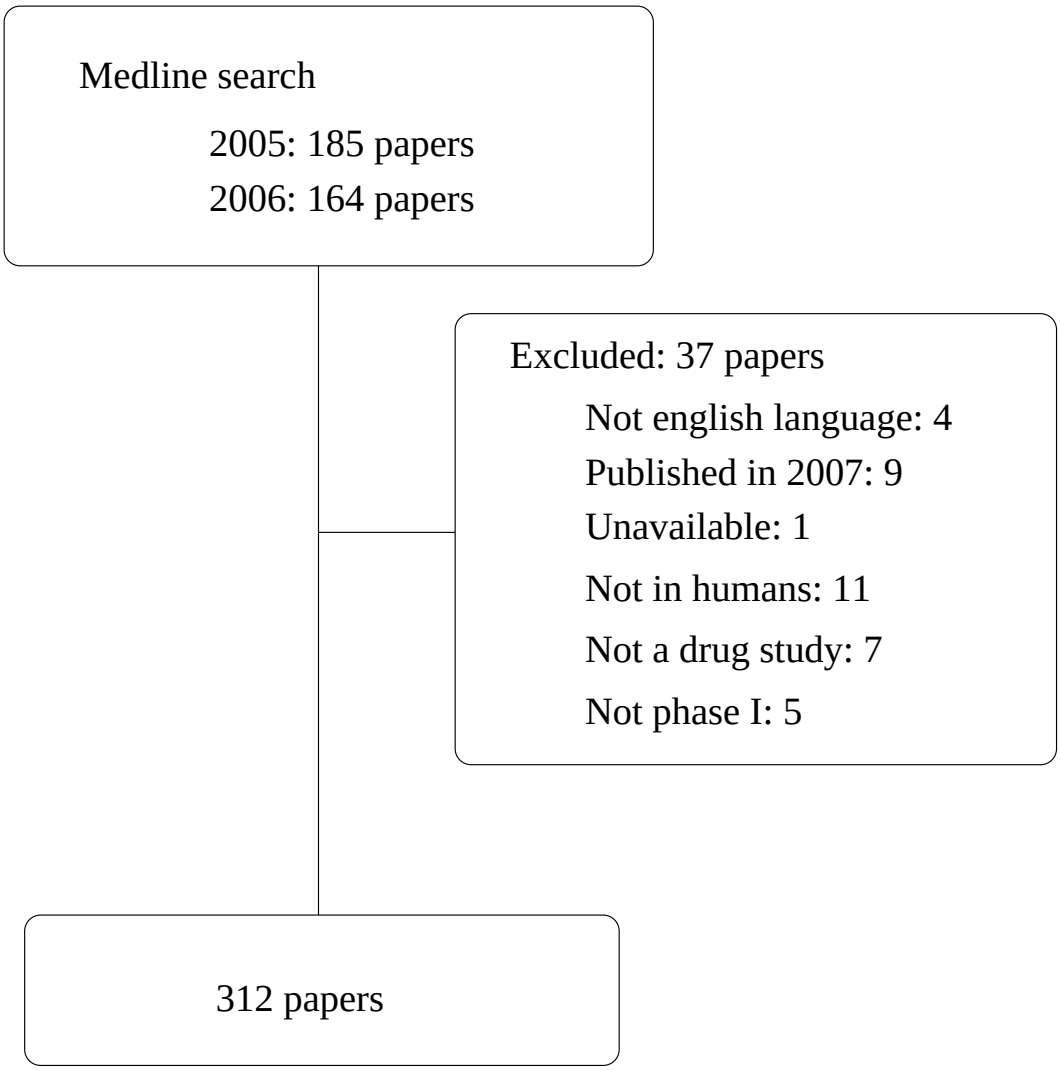
Item		N (%)
Description of PK	yes	248 (88%)
	partial	5 (2%)
	no	30 (10%)
Multiple occasions	yes	183 (65%)
	no	86 (30%)
	Missing	14 (5%)
Analysis method (*)	Descriptive	21 (7%)
	Non compartmental method (NCA)	171 (60%)
	Non linear regression (RNL)	47 (17%)
	Population approach (POP)	9 (3%)
	Not reported	50 (18%)
Model built	yes	48 (17%)
	no	235 (83%)
Relationship PK/toxicity	yes	34 (12%)
	no	246 (87%)
	not applicable	3 (1%)
Relationship PK/efficacy	yes	35 (12%)
	no	241 (85%)
	not applicable	7 (2%)
PK variables (*)	Observed concentrations	34 (12%)
	Cmax, Css, Ctrough,...	196 (69%)
	AUC	224 (79%)
	NCA parameters	173 (61%)
	CL	158 (56%)
	PK parameters	12 (4%)
	Other	42 (15%)
	none reported	13 (5%)

(*) multiple answers possible

Table III : Multiple or single drug, for the pharmacokinetic study reported in the 283 papers concerning oncology trials and including PK.

Item		N (%)
Single drug	yes	163 (52%)
	no	120 (38%)
Interaction study (n=120)	yes	21 (18%)
	no	99 (82%)
Double escalation (n=120)	yes	39 (32%)
	no	81 (68%)
PK studied for associated drugs (n=120)	yes	51 (42%)
	no	69 (58%)
Interaction studied (n=120)	yes	22 (18%)
	partial	26 (22%)
	no	72 (60%)

Figures


Medline search
2005: 185 papers
2006: 164 papers
Excluded: 37 papers
Not english language: 4
Published in 2007: 9
Unavailable: 1
Not in humans: 11
Not a drug study: 7
Not phase I: 5
312 papers