Variability in Human Drug Response
G.T. Tucker, Editor


# Management of Variability – Regulatory Aspects

Tomas Salmonson and Janet R. Wade

Medical Products Agency, Uppsala, Sweden

## ABSTRACT

The aim of this article is to give a very subjective, but regulatory perspective, on the issue of managing variability. It is recognised that the current health care environment favours a "one dose fits all" situation. However, everybody realises that the response in an individual patient to a given dose depends upon a unique combination of factors that can influence both the pharmacokinetics and pharmacodynamics of the drug. The major focus of the article has been placed on the more widely understood factors that influence pharmacokinetics and which can include, food effects, age effects, disease in the eliminating organ, etc. The impact of these factors on both inter- and intra-subject variability is discussed. It should be task of all regulatory agencies to encourage the drug developers to identify the factors that are of clinical relevance and so minimise their impact on inter- and intra-subject variability. Such knowledge could facilitate individualised treatment by recognising that each patient is unique. In this respect the Summary of Product Characteristics (SPC) could be used to a much greater extent to reward knowledge and penalise the opposite.

**Key words**: drug development, pharmacokinetics, drug label.

**Correspondence:** Dr. Tomas Salmonson, Medical Products Agency, P.O. Box 26, S-751 03 Uppsala, Sweden, Tel: +46-18-17-4600, Fax: +46-18-54-8566, Email: Tomas.Salmonson@mpa.se

## INTRODUCTION

The clinical response to a drug in an individual patient depends upon a number of pharmacokinetic and pharmacodynamic variables. It is well recognised that there is both inter- and intra-individual variability in these variables. It would then seem logical that drug developers and the health care system, including regulatory agencies, would do their utmost to understand impact of the variable patient characteristics (such as age, gender and organ function) on and within the pharmacokinetic/pharmacodynamic relationship in order to minimise the variability therein. Such knowledge could facilitate individualised treatment by recognising that each patient is unique.

Today, unfortunately, the opposite situation is favoured in many cases. Any need for dose adjustment between different patient groups, or restrictions regarding the use of the drug (e.g. in relation to food) are perceived by many drug developers to be disadvantageous. A one dose fits all philosophy simplifies the use of the product and this is welcomed by a health care system under pressure. In other words, the health care system does not reward knowledge but rather ignorance. Regulatory agencies are to some extent also responsible for this dilemma by not better penalising companies that do not fully consider factors determining the clinical response in an individual patient. In this respect the Summary of Product Characteristics (SPC) could be used to a much greater degree to reward knowledge and penalise the opposite.

There are, however, reasons to be optimistic about a change in this situation in the future. Incorrect treatment with dose related adverse events or sub-therapeutic doses may be perceived to be, not only a clinical, but also a financial problem. In addition, recognition of some potential sources of variability, such as gender, are becoming politically as well as scientifically driven. As a result, guidelines are being developed within many areas such as drug metabolism, interactions, different age groups and decreased organ functions.

The aim of this paper is to discuss sources of variability in the pharmacokinetics of a drug and indicate how these can be managed from a regulatory point of view. This paper has chosen to focus on pharmacokinetic variability since there is a greater depth of knowledge as to the contributing causes, and so is the place where regulatory agencies today can have the most impact. This however, is only half of the story. Whilst it will not be discussed, is extremely important to bear in mind that variability in pharmacodynamic response to a given drug concentration also determines what magnitude of effect the drug will have. As has already been stated, the variability in pharmacokinetics and pharmacodynamics is comprised of both inter- and intra-subject components. In general, the regulatory agencies have a greater impact on managing inter-subject variability. There are fewer instances where regulatory agencies can impact on intra-subject variability and these will be pointed out.

## SOURCES OF VARIABILITY – EXAMPLES

### Compliance

This is a subject that is discussed elsewhere in this book and will not be considered in depth here, except to acknowledge that compliance, or lack of compliance, will contribute to both inter- and intra-subject variability in response to the drug. It is difficult to see how regulatory agencies could lessen this source of variability. The resolution of problems arising from inadequate compliance has to be dealt with through education of both prescriber and patient.

### Absorption

Food is a well-known factor that can influence the absorption of drugs. In a small survey conducted at the Swedish Medical Products Agency (MPA) a few years ago, food was found to significantly influence the pharmacokinetic parameters in 79% of 33 new chemical entities assessed. Food can influence not only the drug substance itself, but also the dosage form, the behaviour of different theophylline slow-release formulations is an example of this. Consequently regulatory agencies require to know if an observed food effect is the result of

an interaction with either the drug substance or the dosage form. Appropriate recommendations can then be made to the developer of the drug.

The uncertainty of food effects has been recognised by most drug developers and food interaction studies are often performed early in the clinical trial program. Nevertheless, at least two recent phase III programs have, partly or totally, probably failed because the effect of food was not fully considered in the design of the pivotal studies.

A recent example of the influence of food is illustrated in Figures 1 and 2. This drug is currently on its way into phase II. In the clinical trial protocol submitted to MPA two doses

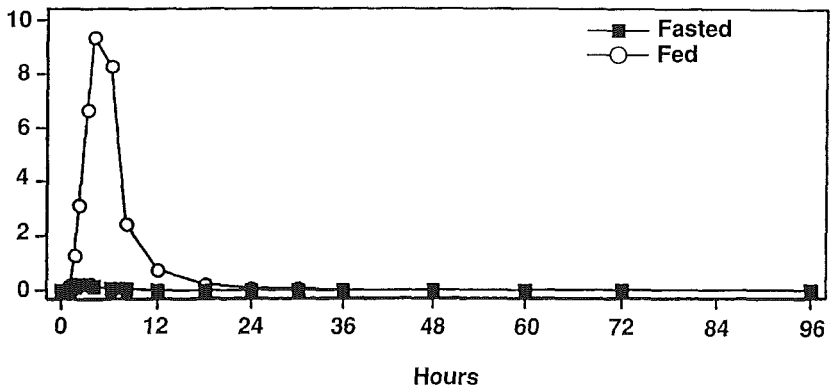


**Figure 1.** The influence of food con the concentration time profile for a drug currently entering phase II

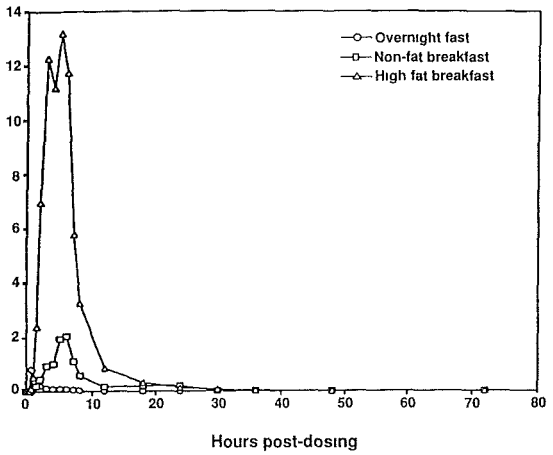


**Figure 2.** The influence of different types of food on the concentration time profile for a drug currently entering phase II

of 50 and 100 mg were to be compared. For a given dose, the difference in the AUC when taken either with a meal, or in a fasted state, is about 50 fold. Even if the company is correct in that the true difference is less because of the formation of an active metabolite, the probability of finding a difference between the two doses seems small given the influence of food.

Controlling whether the drug should be taken with or without food should minimise inter- and intra-subject variability when a food effect is present. Of clinical interest also is the large difference in effect that different types of meals may have (Figure 2). It seems reasonable to assume that this would result in large intra-individual variability if the drug is recommended to be taken with a meal. Such intra-subject variability could be minimised by giving information as to what types of food should or should not be eaten.

The duration of a food effect has, perhaps, been less acknowledged. The effect of a high fat meal can last for more than four hours. A meal could also influence the absorption of drugs taken during a significant window of time prior to the meal. Hence, depending on the habits of an individual patient it may not be possible to avoid a food effect.

**Elimination**

Inter-subject variability in drug metabolism is well-known. The fairly continuous variability associated with CYP3A4 activity and the discrete bands of variability in CYP2D6 activity are examples of this. It will be interesting to see how many CYP2D6 substrates will be developed in the future as drug companies try and minimise the inter-subject variability in response to their products. Tolterodine, a recently approved CYP2D6 substrate, is an interesting example because the applicant demonstrated that, due to the formation of an active metabolite, one dose range could be recommended, regardless of metabolic status. Genotypic expression of metabolic status is certainly a determinant of inter-subject variability. The fact that phenotypic expression may vary and thus contribute to intra-subject variability is an area that has not been possible to regulate thus far.

Drug developers should, and in the main, do, determine the major metabolic routes of elimination for a new drug. In this respect *in vitro* data can often be very valuable when deciding which, and then designing, the *in vivo* studies needed prior to registration. Once the metabolic pathways have been identified the sensitivity to inhibition or induction of the pathway can be tested with inhibitors/inducers. In this way, the risk of other drugs influencing the pharmacokinetics of the new drug can be established. Similarly, *in vitro* and *in vivo* data can be used to predict the potential of the new drug to influence the pharmacokinetics of other drugs. For a more extensive discussion of this topic the reader is referred to guidelines on these issues recently released in Europe and the US. It is hoped that these guidelines will help reduce variability in response due to potential drug interactions. It is also hoped that, in the future, more information will be made available to regulatory agencies as to the duration (onset and offset) of drug interaction effects, thus permitting appropriate dosing recommendations to be made and so minimising intra-subject variability.

Studies in patients with decrease organ failure have, for a long time, been a part of a standard drug development program. However, the impression can be gained that these studies are performed only to satisfy regulatory agencies. For example, the value of many studies in patients with decreased liver function could be questioned. It is important that more is learnt about how different enzymes are influenced by different types of liver impairment. The frequently used Child-Pugh scoring system, whilst at least giving some indication as to the

degree of impairment, is probably not be the best way to grade the capacity of the different metabolic enzymes and more appropriate methods need to be developed.

The analysis of the results from these studies in organ impairment can also sometimes be questioned. This can be illustrated by that in studies in decreased renal failure, patients are often grouped together in what are fairly arbitrarily chosen ranges. One such example of this is shown in Table 1. When used to stratify patients for dosage recommendations theses ranges are, of course, valuable. However, there is no reason to use such categorisations when analysing the results. Use of the (continuous) individual values for creatinine clearance and the corresponding observed AUC estimates should, in many cases, increase the value of the results.

**Table 1.**
An example of grouping of patients with impaired organ function into arbitrarily chosen categories.

| | Cretatinine Clearance (ml/min) | | | |
|---|---|---|---|---|
| Parameter | >90 (n=4) | 66-90 (n=4) | 41-65 (n=5) | 10-40 (n=8) |
| $C_{max}$ | 17±10 | 24±10 | 18±12 | 26±18 |
| $AUC_{0-t}$ (ng.h/ml) | 150±57<br>84-204 | 148±31<br>127-193 | 166±38<br>108-215 | 268±152<br>106-516 |

The fact of presence or absence of disease in an eliminating organ is a factor determining the magnitude of the inter-subject variability. However, a disease state is a process that may get better, remain the same, or degenerate, all changes which will impact on the intra-subject variability. It is important that the prescriber is given information that will enable doses to be adjusted at appropriate times with respect to degree of impairment.

**Patient characteristics**

Studies in elderly are often part of a drug development program. Granted the ageing population and their extensive use of drugs, this is not only justifiable but necessary. Given the increase in life expectancy one could sometimes, perhaps, question the value of studies in patients of only 65-75 years of age. Subjects included in these studies are often relatively healthy and probably display only a minor decrease in renal function compared with a younger population. The results obtained will, therefore, underestimate the true impact of age on inter-subject variability.

Potential gender differences should also be studied. Differences are found in the pharmacokinetics between men and women far more often than result in different dosing

recommendations. One reason for this could be that the observed difference lacks clinical significance. But how do we know that? Separate dose finding studies are seldom performed and phase III studies are not powered to detect a difference in adverse events or lack of effect between these two groups. Some of the new anti-migraine products are examples of this. The AUC in women is twice that observed in men. This disease is common in women and phase II and III studies often include many women. One can speculate that either the women are given a too high dose or, probably more likely, the men receive too low a dose.

The effect of weight is another often neglected factor. In an recent application for a new AIDS drug it was shown that trough plasma levels above 3.5 M were desirable to maintain the clinical efficacy and to possibly reduce the risk of tolerance development. It is apparent from Table 2 that many patients with an exposure below the desired concentration range were heavier than the groups with higher plasma levels. This was not perceived by the applicant to be of clinical significance. Hence, the company has applied for the same dose for all patients, which is surprising given the seriousness of the indication and the consequences of a sub-optimal treatment.

**Table 2.**
The relationship between weight and trough plasma concentration for a new AIDS drug.

| | Trough concentration windows | | | |
|---|---|---|---|---|
| | <3,5 μM | 3,5 to 7.0 μM | >7.0 μM | All data |
| n | 32 | 81 | 39 | 152 |
| CL/F (L/h) | 16.3±1.6 | 11.7±1.6 | 6.8±1.7 | 11.4±3.6 |
| Weight (kg) | 90±17 | 79±14 | 75±14 | 81±16 |

Age and gender are not usually factors that alter during the course of a single study, and thus contribute more to inter-subject rather than intra-subject variability. This is not the case for weight, where, in serious disease states/processes, it is quite conceivable that a patients' weight may decrease as the condition worsens, or increase as the patient gets better. Should a drugs pharmacokinetics be dependent upon weight, then altering the dose in accordance with weight changes seems a fairly simple way of managing the consequent intra-subject variability.

**Social habits**

The effect of grapefruit juice on many CYP3A4 substrates has made us aware that dietary habits may influence the response to drug treatment. Smoking is another factor well-known to influence certain drugs. An example of a factor that has been less well studied is pharmacokinetics in vegetarians. All these social factors need not remain constant in a given patient during a course of treatment. An understanding of the impact of these factors is certainly a case where regulators can and do have an impact on minimising intra-subject variability.

## APPLICABILITY OF PHASE III DATA

In order to maximise the possibility of achieving conclusive, confirmatory results, phase II and III studies are often designed to minimise the inter-subject variability. One could speculate that the increased number of exclusion criteria observed in clinical trials conducted in Sweden is a result of this (Figure 3). Thus, the studied population is a selection of patients that will not entirely represent the intended target population. Information generated from phase I or pre-clinical studies are later used to generalise the clinical results obtained to the wider group of patients covered by indication applied for.

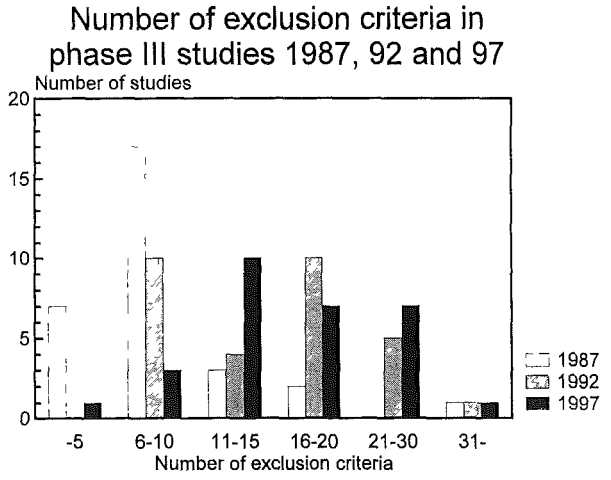


**Figure 3.** Number of exclusion criteria in protocols for phase III studies 1987, 92 and 97 submitted to the MPA

It appears as if drug developers find it easier to accept corrections for some sources of variability more than others. For example, industry and regulators often accept dose corrections in patients with decreased renal function based on pharmacokinetic data. If it is unknown whether AUC or Cmax (or another composite measure) is best correlated to the dynamic endpoint in question (and one ends up with different dosing recommendations depending on which pharmacokinetic variable chosen), then the risk of sub-therapeutic doses versus the risk of dose-related ADRs has to guide the dose selection.

Despite the arguments presented above, to convince an applicant of the need for a correction for other sources of variability such as gender effects or even food (if such an effect was not considered in the design of the study) is difficult. The applicant often argues that significant results were obtained in the phase III studies without correction for these sources of variability and that there were no differences in adverse events between, for example, men and women. Such an argument does not consider that the study, in this respect, was probably underpowered, and so is unconvincing for the regulatory agencies.

Another consideration seldom (if ever) acknowledged is the possibility of an altered concentration-effect relationship in different patients. The general lack of PK/PD information

in the package submitted to the regulatory agencies prevents us from addressing this. In all cases when agencies try and correct for factors that contribute to inter-subject variability, an underlying assumption has to be made that the concentration-effect relationship in the different patient groups is the same. This certainly does not have to be the case. Wade and Sambol (1995) showed that not only do the elderly display increased felodipine plasma levels for a given dose of the drug, but even for the same plasma concentration, a greater response is observed than for a younger patient. Thus providing dosing instructions that correct only for the decrease in clearance observed in the elderly, but do not correct for the attenuated response observed, are clearly not optimal.

## DOSE SELECTION

The selection of recommended dose/dose range is often an interesting challenge. The dose proposed by the applicant must be evaluated by the regulatory authority. Some of the new anti-migraine drugs can be used to illustrate this.

For one of the newer "triptans" a five-fold difference was found in the AUC values for a group of healthy volunteers (large inter-subject variability). The estimated (assuming dose-linearity) intra-individual variability was much less. Dose-response studies showed that a doubling of the dose within the suggested dose range increased the number of patients free from pain after 2 hours by only a few percent. The available concentration-effect data indicated that the variability in this relationship was relatively small. Based on these data some argued that the lower dose should be recommended (or even half of it), and possibly, for patients not responding during the first attack, a higher dose could be taken in subsequent attacks. Others believed that the dose related ADRs for the highest dose were acceptable and concluded with the argument that there was an intra-individual variability in the severity of the attacks (and thereby variability in the need of pain-relief), and so the highest dose should be given to all patients.

Regardless of which view one subscribes to, the above discussion illustrates many of the factors that need to considered when deciding upon dosing recommendations.

## LABELLING

The documented characteristics of a drug should be described in the SPC. It is important that drug labelling rewards the applicants who have investigated sources of variability and not the opposite. The newly adopted European paediatric guideline allows the inclusion of pharmacokinetic information for children in the SPC, even if there are no, or insufficient, clinical data to include this age group in the indication/posology. It is hoped that this guideline will encourage applicants to perform pharmacokinetic studies in children so that the drug can ultimately be prescribed for this patient group at an earlier point in time than is currently the case. Having said that, contra-indicating patient groups which have not been studied but for whom there is no reason to suspect that they have different pharmacokinetics seems questionable. Such a course of action could put a prescriber with no other treatment options in a difficult position.

On the other hand, there is sometimes a tendency by regulators to pretend that we know more than we do. The often general dosing recommendations for patients with decreased liver function are an example of this It would seem better to avoid general terms such as

"moderately impaired liver function" and, instead, describe the actual patients studied in more detail. Similar arguments can be made within the area of drug interactions where it is sometimes difficult to extrapolate to doses other than those studied. Such a course of action could be viewed as the regulatory agencies avoiding their responsibilities, but surely it is preferable that the prescriber, with their more intimate knowledge of the individual patient, makes the best informed decision possible, rather than relying on educated guess work from the regulatory agencies.

## CONCLUSION

The aim of this article has been to give a very subjective, but regulatory perspective, on the issue of managing inter- and intra-subject variability. It is recognised that the current health care environment favours a "one dose fits all" situation. However, everybody realises that the response in an individual patient to a given dose depends upon a unique combination of factors that can influence both the pharmacokinetics and pharmacodynamics of the drug. It should be task of all regulatory agencies to encourage the drug developers to identify the factors that are of clinical relevance and so minimise their impact on inter- and intra-subject variability. Furthermore, the information obtained should be described in the SPC and so permit the prescriber to treat each individual patient in the best clinical and, perhaps also, cost-effective manner.

## REFERENCES

1. Wade, JR, & Sambol, NC. Felodipine population dose-response and concentration - response in patients with essential hypertension. Clin Pharmacol Ther 1995;57:569-581.

**Discussion: Management of variability - Regulatory aspects**

**A. Breckenridge:**

I wonder if you share that, in drug regulation, we tend to concentrate up on factors relating to inter-individual variability and efficacy. Perhaps at the expense of issues concerning safety. This may well be because safety is considered a post-licensing problem, but it does seem that the emphasis is perhaps slightly in the wrong direction.

**T. Salmonson:**

There are many reasons for that. For example, the assessors are often experts at their own area. They focus on efficacy, because that is what they are interested in. I think one could speculate that one reason why Posicor was so happily accepted in the US and in the rest of Europe was because they already assumed that some of the ongoing trials were coming up favourably. We are focusing a lot on efficacy and not on safety, which is very ridiculous. I believe that we sometimes could leave the efficacy-establishing issue to the clinicians. But to judge for safety, in overall relation you need a larger group of patients and you need a type of qualification and knowledge, which perhaps the prescribing physician does not have.

**C. Martínez:**

I have a question concerning the study population and target population. And I fully understand that by the selection criteria that we have, the study population would go more away from being representative of the target population, which would probably increase the power of the study because of lower variability. If we go back to the animal studies, what we have are inbred strains of rats, from those we achieve specific conclusions. Do you think we should go back and have a random sample of the rats?

**T. Salmonson:**

No, I guess not. When in rats you are trying to establish and look at only one thing, it creates no problem. But if you want to look for something that you do not know, like safety for instance, it becomes very difficult to generalise. You can use the same argument when we perform population studies in a group of people, which is not really representative. There are a lot of problems, like the cost-related ones due to the enormous requirements in the development of the new drugs. So it is understandable why they are trying to limit these studies.

**H.K. Kroemer:**

I am interested in getting a statement on how in the long-term you handle the food issue, because it is turning out to be an important point. I recall a publication from Canada about single-dose administration of propafenone, in which they could show that food made an interaction only in extensive metabolisers, as a result of a CYP2D6 inhibition. When you asked them to do the same in a steady state, they tell you that they did not see any effect, although they never published that. In general, you can have very nice and dramatic effects for single administration, but you may not be able to solve or clarify with other studies. Finally, in real life you never will be able to adjust drug-doses for food intake in all the people. Therefore, I would like to know how you plan in the long term to deal with this issue.

**T. Salmonson:**

I think you are absolutely right. The food interaction most often decreases when you analyse it under steady state conditions. That is why many companies do it as planned, and if there is still an effect they investigate the effect under steady state conditions. Often there is no way you can practically avoid a food effect, because a food effect is there for a very long time. As we saw in the AIDS example, I would rather say take it with food and have that little restriction.

**H.K. Kroemer:**

But how do you deal with it in a practical way? People are likely to say to you, like the previous example, that there is an extreme difference, whether you take it with food or not. Is there a point where you would reject a drug, based on data like that?

**T. Salmonson:**

Yes, there is such a point. We have a recent example where a drug may be rejected because there is a dramatic, clinically relevant food effect. It is a three times daily drug. Some people argue that you cannot launch a drug with that type of characteristics. The extreme example I showed you was a clinical trial, where we just put a question-mark regarding the doubling of the dose and in real life it may be impossible to avoid it regardless how you write the labelling compared to the huge variability that one would expect, given the magnitude of the food effect and the effect of different types of food.

**D.A. Smith:**

That was the reason why it was something to be dealt with in the design stage, because it is almost impossible once you have put it into development to do anything about it. It is something which is actually doable at that stage, to actually incorporate it in your drug discovery programme. I would just like to throw in the thought that most drugs are not taken individually, but they are normally taken in combination. The biggest disadvantage is when you have to take one drug with food and the other after the food, or three hours after. This is a situation almost impossible to comply, which is the case with AIDS therapy, where you are taking multiple tablets throughout the day.

**T. Salmonson:**

You are absolutely right. You can have a food effect for four hours after the meal. So, it is impossible to avoid a food effect for a drug that you take three times a day.