

# 1 Early Phase Trials

## 1.1 INTRODUCTION

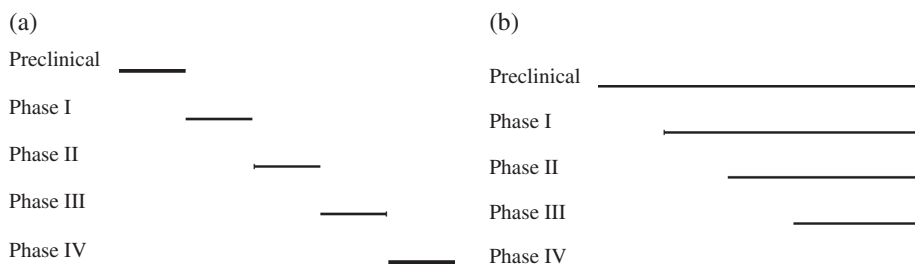
Trials conducted in the early phases of the molecule-to-marketplace clinical development paradigm take compounds from first time into man through to the start of the pivotal clinical trial programme. These early phases could be considered to be the learning and explaining phases. They are learning as by definition there is no experience of the compound in man when starting these studies and many important factors relevant to a compound's development will need to be quantified. They are explaining as early trials help to describe the properties of the compound, inputting to its rationale.

Although it is only in late-phase development that definitive proof can be obtained, early phase studies are important as they inform some of the most important decisions in a clinical programme, such as the most appropriate dose to carry forward, and the posology. They also contribute to important factors such the inclusion/exclusion criteria for a compound with respect to late-phase protocols' populations (or labelling). For the inclusion/exclusion criteria, without sufficient enabling studies these may be so tight as to make recruitment rates impracticably slow.

By definition in early drug development there is little information available when designing trials, and resource is often constrained both financially and in terms of populations available to recruit. These factors can have a major impact on the design and conduct of the trials, with innovative and adaptive designs often being applied as a way of overcoming the restrictions. However, in early phase trials, what is lacking in resource can, in part, be made up for by increased control, for example the trialists themselves control the rate of recruitment in a healthy volunteer study. In addition, early trials often are more tightly controlled with respect to more restricted populations from smaller pools of specialist centres. This can positively benefit statistical variability, enabling smaller signals to be detected from these smaller studies.

## 1.2 DEFINITIONS OF THE PHASES OF EARLY DEVELOPMENT

The naive view of the phases of clinical development is that they follow a chronological ordering of the form described in Figure 1.1a. In this ordering the distinct phases are like batons in a relay race. Initially a compound is picked up in a preclinical setting by



**Figure 1.1** Perception of the phases of drug development.

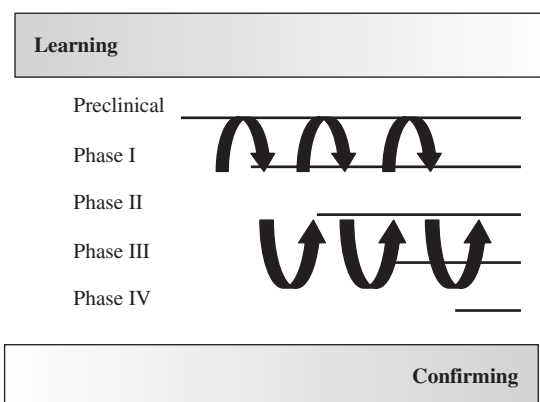
researchers, where work is undertaken until a point is reached when it can be handed on to Phase I. Phase I researchers then take on the baton and run with it until they can hand it on to Phase II and so on.

The ordering of the phases is better described in Figure 1.1b. Here what actually happens in clinical development is that the minimum body of work is done in each phase before the compound progresses to the next phase. The consequence is that much of what would be considered early phase trials actually takes place when a compound is late in development. This minimum body of work is usually referred to as critical-path activities. Hence, where Figure 1.1a can be considered to be accurate is that it figuratively describes these critical-path studies.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topic E8 gives a detailed description of the phases of development (ICH, 1998a), while the Food and Drug Administration (FDA, 2006a) defines the critical path and what we learn along the way as follows:

At the start of the Critical Path, developers form hypotheses about performance characteristics such as safety, biological or mechanical action, and biocompatibility. They then seek to evaluate and confirm these hypotheses using *in vitro*, animal, and human testing. Once uncertainty about benefits and risks of a product has been reduced to an acceptable level, the product may be approved for marketing—if the benefits outweigh the risks. The great challenge in development lies in predicting a potential product’s performance as early as possible with the greatest degree of certainty.

With this definition, in terms of studies necessary for filing registration, all studies fall along the critical path. However, it can be argued that critical-path studies are just those that drive the development timelines and must be done prior to the start of subsequent activities. Studies that can be done in parallel with other activities, that is, that must be done but not before some pre-prescribed critical path task, are termed non-critical path. As an aside, in this context given that much preclinical work happens when a compound is actually in clinical development there is an argument that ‘phase 0’ as opposed to ‘preclinical’ may be a more accurate nomenclature.



**Figure 1.2** Interweaving of the phases of drug development.

For a given compound, therefore, activities in a clinical plan may look like Figure 1.2, moving between learning and confirming, and where critical-path activities preclinically may be triggered by activities in Phase I and vice versa. A compound may also move along the different phases according to different indications or populations for which it may be being targeted.

Due to the wide variety of work undertaken in early phase development, generic definition of the early phases is not really possible. Simply it can be said that Phase I is performed in healthy volunteers and is the phase where safety and tolerability are assessed, while Phase II is undertaken in patients and is the phase where the first assessment of efficacy is made. However, things are not as simple as these definitions imply. In therapeutic areas such as oncology, Phase I may be undertaken in patients, while for certain areas, the size and scale of Phase II may resemble Phase III for other areas.

In truth what can be stated is that a compound must go first time into man (FTIM), and that some time after this study the pivotal Phase III programme must start. From the point of the start of FTIM to the start of the pivotal Phase III programme we can define as early phase development (in addition of course to the early phase work being undertaken in parallel to Phase III).

Subsequent chapters will detail the different types of early phase trials.

### 1.3 CLINICAL DEVELOPMENT PLANS

When taking a compound from molecule to marketplace it could be argued that the vast majority of studies would fall under the banner of early phase. This greater number of studies equates to a greater variety of types of studies that can be undertaken, from routine ‘bleed them and feed them’ type studies – for example studies to assess drug or food interactions – through to innovative designs. The trials themselves are undertaken in a

**Table 1.1** Definition of critical-path and non-critical-path activities

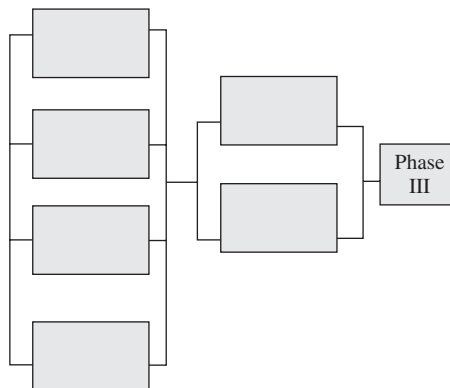
Critical path	Non-critical path
Studies that must be undertaken prior to the start of subsequent activities	Studies that need to be done but not before some pre-prescribed critical path task
Drive the development timelines	Can be done in parallel
Examples: first time into man; repeat dose study	Examples: pharmacokinetic- or pharmacodynamic-interaction studies

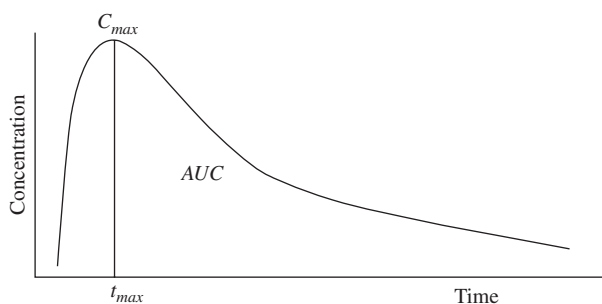
number of populations. Initially these trial populations will most likely be of healthy volunteers before moving into patient populations and maybe subpopulations within these patient populations.

To coordinate all these activities a clinical development plan (CDP) needs to be drafted. This document will be needed to help coordinate the activities, critical path and non-critical path, required for development. The focus initially will be on the critical-path activities, as defined in Table 1.1, as these will determine timelines, whilst non-critical-path activities could be completed in parallel.

Examples of critical-path studies are the first-time-in-man study (which obviously must be done), maybe followed by the repeat-dose study for a chronic intervention. Obviously a compound must be shown to be safe and tolerable in a single-dose study before it can be given in a repeat-dose study. Other studies may follow in sequential order to these.

Examples of non-critical-path activities could be studies to investigate possible pharmacokinetic interaction or pharmacodynamic interactions. These may not fall on the critical path but would need to be done prior to the start of the pivotal programme, as without them the protocol inclusion criteria would be affected and as a consequence the rate of recruitment. Figure 1.3 gives an illustration of how a clinical development plan may be summarized.

**Figure 1.3** Typical clinical development plan from early stages to start of Phase III.



**Figure 1.4** Example of an individual extravascular pharmacokinetic profile.

## 1.4 PHARMACOKINETICS

A main aim of many early phase studies is to assess the pharmacokinetic (PK) activity of a given compound. This is often referred to as analysing the effect of the body on the drug. This is achieved by the derivation of a concentration–time profile for each individual given the compound. Figure 1.4 gives an illustrative example of a hypothetical extravascular pharmacokinetic profile (to be discussed in more detail in Chapter 2).

In truth an analysis of the full pharmacokinetic profile is not usually undertaken but instead appropriate summary statistics are used to assess the pharmacokinetics. This assessment is usually performed by determining the extent and rate of absorption, using the AUC (area under the concentration curve) to assess the extent of absorption and the  $C_{\max}$  (maximum concentration) to assess the rate of absorption (see Figure 1.4).

Other summary measures that could be used include time to maximum concentration ( $t_{\max}$ ) and the time taken for the apparent terminal plasma concentration to fall by one half (half-life,  $t_{1/2}$ ). This half-life is often used to determine the dose schedule for a given compound. A short half-life will require regular dosing, whilst a longer half-life will require less-frequent dosing.

Once appropriate pharmacokinetic summary parameters are derived for each individual, then inferences across subjects in the study may be drawn through descriptive statistics (for a given dose). Initially only single doses will be given to assess the pharmacokinetics, which if shown to be tolerable will lead to repeat dosing and repeat-dose pharmacokinetics (depending on the indication). However, the single-dose pharmacokinetics is key information, as from these data it is possible, under certain assumptions, to predict the repeat-dose profiles.

Usually, in the very early stages of development, full pharmacokinetic profiles are collected on a tightly controlled, relatively small number of healthy volunteers, in studies which have a main aim of assessing these profiles. For studies later in development, pharmacokinetic information may be obtained on a patient population but it may no longer be a main aim for the individual study – indeed it may now be a substudy to the main study. For such studies, instead of taking full profiles on individuals, sparser pharmacokinetic sampling may be performed. However, these data could be obtained on a larger

sample size, and the sparse sampling from individuals at time points across the pharmacokinetic time frame may enable full profiles to be quantified.

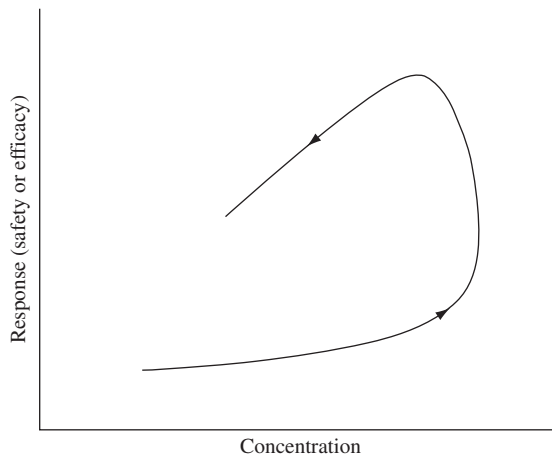
Chapter 2 will go into greater detail on pharmacokinetics.

## 1.5 PHARMACODYNAMICS

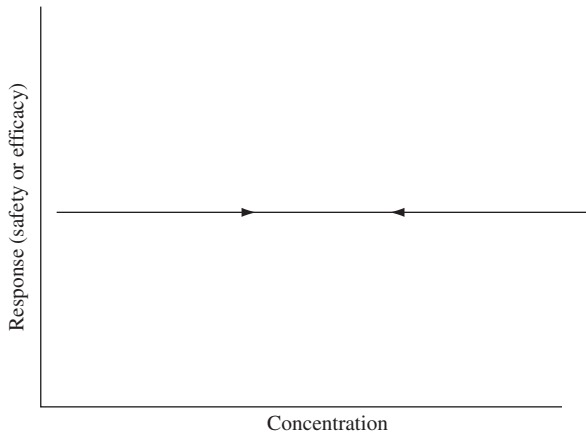
Pharmacodynamics (PD) is the analysis of the effect of the drug on the body in terms of both safety and efficacy. In drug development, initially the emphasis is on safety, before moving onto efficacy later. This simplistic definition holds as, depending on indication, studies are conducted initially just in healthy volunteers (to assess safety and tolerability) before moving into patients later (to assess efficacy). However, it is a little too simplistic, as efficacy can be assessed to a degree in healthy volunteers, whilst it could be argued that only in later, and larger, patient trials can safety truly be assessed.

Similarly to pharmacokinetics, pharmacodynamic responses, such as those from efficacy outcomes, biomarker data or a surrogate endpoint in early trials, can be summarized through statistics such as the pharmacodynamic half-life. This half-life could in turn be used to determine dosing schedule.

In addition to assessing the pharmacodynamics and pharmacokinetics independently, PK/PD modelling can be undertaken – which again may inform decisions on dosing schedule. Figure 1.5 gives an illustration of what an indirect response may look like when linking pharmacodynamics with pharmacokinetics for a single dose. The loop (termed a hysteresis loop) indicates how the same level of drug could illicit different responses, dependent on the time relative to dose that the response was assessed. Here you need to know time as well as concentration to be able to predict the effect.



**Figure 1.5** Indirect relationship between response and pharmacokinetics for a single dose.



**Figure 1.6** Relationship between response and pharmacokinetics after repeat doses.

This could be compared to an illustrative (hoped for) PK/PD relationship from after repeat dosing, given in Figure 1.6, where the PD response is constant relative to both time and the pharmacokinetics.

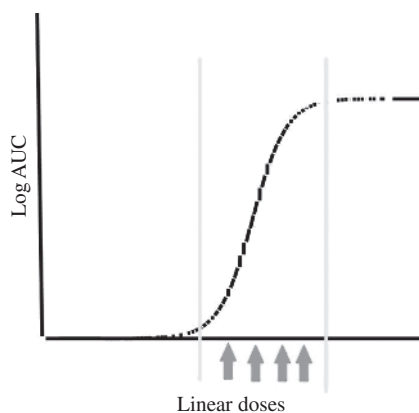
In terms of drug development, it is important to quantify any relationship between exposure and safety and/or efficacy throughout the development process. For example, the US Food and Drug Administration (FDA, 2003) stated that, for meetings between the regulators and developers at the end of the early stages of Phase II development (Phase IIa):

The overall purpose of these meetings is to discuss the exposure response information during early drug development. The exposure response will be pertinent to both favorable (*sic*) and adverse effects.

## 1.6 DOSE PROPORTIONALITY

Probably one of the most important assumptions (or properties) in drug development is that of dose proportionality. Figure 1.7 gives an illustrative example of what the pharmacokinetics (in terms, here, of AUC) across a dose range may look like. The wish would be to concentrate future dose selections in clinical outcome studies on the linear part of the dose curve. This is because after a point in this example, increasing dose does not equate to increasing amount-of-drug concentration, and thus there is unlikely to be any benefit from these higher doses.

Dose proportionality would be assessed preliminarily in the first-into-man study before a later definitive study is performed. Having dose-proportional pharmacokinetics is important, as not only does this assumption drive dose selection in patient studies but it also effects



**Figure 1.7** Anticipated relationship between pharmacokinetic AUC and dose.

decisions such as those of dose adjustments for special populations, and also underpins prediction of repeat-dose pharmacokinetics and interpolation in PK/PD modelling.

Without dose proportionality a compound could still be viable. However, there are consequent complications. Not only does it impact on the analyses described above but it can also complicate bioequivalence studies, for example, which may need to be undertaken with several doses.

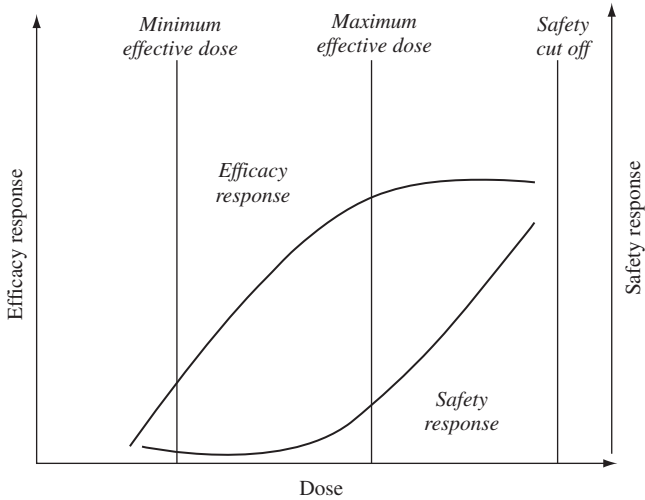
Chapters 2, 8 and 10 give details on dose proportionality in the context of drug development, as well as how to design and analyse studies to make the assessment.

## 1.7 DOSE RESPONSE

The context of dose here is in terms of clinical response both for efficacy and for safety. The selection of dose is important; too low and the compound could be proceeding with a suboptimal level of efficacy; too high and unnecessary tolerability concerns may become an issue.

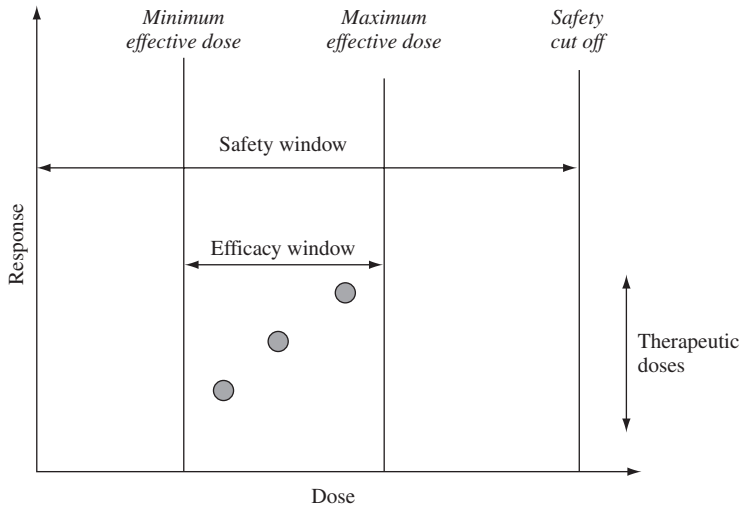
Figure 1.8 illustrates the points considered in dose response. This figure is a little naughty in that it has two response axes in the same graph, but it does summarize the considerations nicely. It illustrates a scenario where after a given dose there is no additional clinical benefit but the number of adverse responses is greatly increasing. This dose is referred to as the maximum effective dose (MED), and in adjudicating on harm, a decision on doses beyond this would tend to be against their selection.

Initially the safety cut off would have come from animal data and would be based on a fraction of the dose given to the most sensitive animal – often referred to as the no-observed-effect level (NOEL). After proceeding with drug development, however, this may relate to the maximum tolerated dose (MTD) given to man. This maximum dose could be different in different populations; for example the MTD in healthy volunteers could be considerably lower than that for patients, in certain indications.

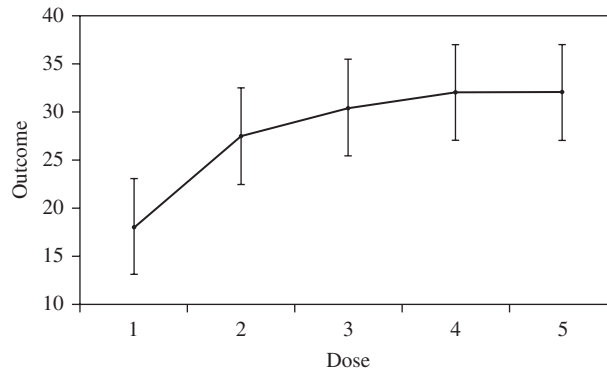


**Figure 1.8** Anticipated relationship of dose response with safety and efficacy.

The dose range up to the safety cut off is referred to as the safety window – as highlighted in Figure 1.9. The wish is to have this window as wide as possible, as a compound could be misused or abused, or there may be unanticipated pharmacodynamic or pharmacokinetic interactions in the subsequent trial populations. Another consideration is absentmindedness, with patients forgetting they have taken their medication already and hence taking it twice. In double-dummy randomized controlled trials there



**Figure 1.9** Dose response, with definitions of safety and efficacy windows.



**Figure 1.10** Dose response assessed by difference from placebo.

can be evidential support of absentmindedness from tablet count data. Hence, it is beneficial to have as big a safety window as possible.

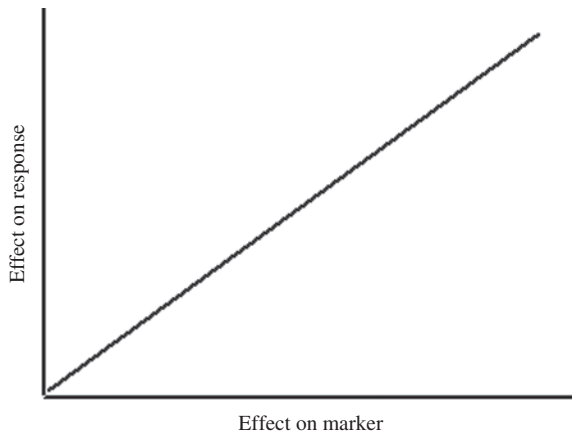
In terms of clinical response to treatment as well as the maximum tolerated dose, the minimum effective and maximum effective dose need to be determined. The distance between the minimum effective and maximum effective dose is termed the efficacy window (see Figure 1.8 and Figure 1.9).

When designing trials to assess dose response it is optimal to select doses falling within this range, as illustrated by the three dots in Figure 1.9. Of course doses are not selected outside of this range on purpose, but often it is hard to judge what the efficacy window is. Figure 1.10 illustrates this point. Does the outcome plateau after dose 4, or is it randomly scattered about a true linear response? Dose selection is difficult and, in the case of the scenario given in Figure 1.10, if the response is truly linear (but dose 4 is carried forward) it could lead to smaller effects being observed in Phase III compared to Phase II.

Subsequent chapters, but in particular Chapters 6 and 12, go into detail on the issues associated with dose response.

## 1.8 GO/NO GO AND INVESTMENT DECISIONS

Before the start of, and investment in, the late phase pivotal programme, a Go/No-Go decision must be made based on the studies undertaken to date. To assist in this decision an adjudication needs to be made as to whether there has been sufficient proof of concept (or efficacy) for a given asset. Primarily the determination of proof of concept would be through an assessment of efficacy. Ideally this would be done through an outcome used in late-phase development, but proof of concept may come from a short-duration study, a biomarker or a surrogate such that actual clinical response is predictable as illustrated in Figure 1.11. However, the adjudication of proof of concept will not be one single item but would be a package linking work on the dose response, safety window, efficacy window and also aspects such as if it is possible to viably formulate or store the compound being developed.

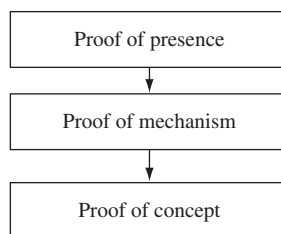


**Figure 1.11** Linking later clinical responses with responses on a marker.

The definition of ‘proof’ in the context of drug development of course varies. ‘Definitive’ here means to provide convincing proof to a sceptic arbiter. Usually this would be a regulatory agency on behalf of society as a whole. Initially, however, the arbiter would be the sponsor of the clinical programme itself. As a consequence the level of proof required from early phase studies is to facilitate appropriate decisions such as Go/No Go and investment decisions.

Of course, just because the level of proof is for an internal arbiter does not mean that the rigour required is any less. However, the context may be in terms of risk discharged through the programme. The sponsor will wish to maximize risk discharged as early as possible in the programme, as a fast-fail decision for an individual compound could free resource and speed development for other compounds in the portfolio. These fast-fail decisions could be made (or facilitated) through assessing whether there has been proof of presence for a compound – determining if the drug gets to the site of action – or if there has been proof of mechanism – determining if the compound affects the *a-priori* hypothesized mechanism for efficacy. There is a logical hierarchy of different types of proof, as illustrated in Figure 1.12, such that with a proven mechanism for a compound, proof of concept may be achieved through proof of presence or through proof of mechanism.

Chapter 15 describes how Go/No-Go criteria may be formed.



**Figure 1.12** Hierarchy of proof.

## 1.9 SUMMARY OF EARLY PHASE TRIAL OBJECTIVES

Early phase studies are studies that enable, enhance and explain a particular compound for a development programme, helping to determine features such as the efficacy and safety windows. There are numerous pros and cons of studies in these early phases. The primary pros being that the studies are often tightly controlled, undertaken in specialist centres and allow the use of often quite creative design. The primary cons are that they have limited resource, which often necessitates creative designs to optimize the information we can get within the fixed limits.

Prior to the start of the late-phase pivotal programme, early phase trials should have determined the dose, the dosing schedule and allowed sufficient risk to be discharged to minimize the chance of a late-phase (expensive) failure.

In particular, after Phase I the programme should have

1. Quantified a range of safe (and potentially efficacious) doses – including the maximum tolerated dose (MTD).
2. Described pharmacokinetic exposure levels of each dose.
3. Facilitated the choice of dose and posology (dose titration, dose interval for later studies).
4. Described the pharmacodynamics at each dose (including biomarkers and surrogates).
5. Developed initial models for use in PK/PD modelling, including efficacy– and safety–exposure.

While at the end of Phase II the programme should have

1. Established the efficacy and safety windows in the target population, including
  - (i) The minimum effective dose
  - (ii) The maximum effective dose
  - (iii) The maximum tolerated dose.
2. Identified the time interval needed to see efficacy or tolerability effects.
3. Provided the dose and schedule for dosing for Phase III, including
  - (i) Response-guided titration steps
  - (ii) Dosing intervals.
4. Developed a model for use in PK/PD modelling including efficacy– and safety–exposure.
5. Identified potential subgroups to be studied for dose adjustment in Phase III (e.g. age, gender).

It must again be highlighted, however, that the different phases of development are not mutually exclusive; early phase trials will continue whilst a compound is in late-phase development to further assist and facilitate in the compound's development.