identified.... If degradation occurs, the chemical reaction kinetics of the degradation should be determined.... Physical changes such as changes from one polymorph to another polymorph should be examined.... With the drug substance stability profile thus completed, the information should be submitted in the IND submission.

2. TIMING AND GOALS OF PREFORMULATION

The goals of the program are therefore (1) to establish the necessary physicochemical parameters of a new drug substance, (2) to determine its kinetic rate profile, (3) to establish its physical characteristics, and (4) to establish its compatibility with common excipients.

To view these in their correct perspective, it is worthwhile to consider when, in an overall industrial program, preformulation takes place. The following events take place between the birth of a new drug substance and its eventual marketing (it is a fact, however, that most investigational drug substances never make it to the marketplace for one reason or another):

1. The drug is synthesized and tested in a pharmacological screen.
2. The drug is found sufficiently interesting to warrant further study.
3. Sufficient quantity is synthesized to (a) perform initial toxicity studies, (b) do initial analytical work, and (c) do initial preformulation.
4. Once past initial toxicity, phase I (clinical pharmacology) begins and there is a need for actual formulations (although the dose level may not yet be determined).
5. Phase II and III clinical testing then follows, and during this phase (preferably phase II) an order of magnitude formula is finalized.
6. After completion of the above, an NDA is submitted.
7. After approval of the NDA, production can start (product launch).

3. PHYSICOCHEMICAL PARAMETERS

Physicochemical studies are usually associated with great precision and accuracy, and in the case of a new drug substance would include studies of (a) $pK_{(a)}$ (if the drug substance is an acid or base), (b) solubility, (c) melting point and polymorphism, (d) vapor pressure (enthalpy of vaporization), (e) surface characteristics (surface area, particle shape, pore volume), and (f) hygroscopicity. Unlike in the usual physicochemical studies, an abundance of material is usually not at hand for the first preformulation studies: in fact, at the time this function starts, precious little material is supplied, and therefore the formulator will often settle for good estimates rather than attempt to generate results with four significant figures.

There is another good reason not to aim too high in the physicochemical studies of the first sample of drug substance. In most cases the synthesis is only a first scheme, and in later scale-up it will be refined; and in general the first small samples contain some small amount of impurities, which may influence the precision of the determined constants. But it is necessary to know, *grosso modo*, important properties such as solubility, pK, and stability. These are dealt with in order below.