on the Fibonacci sequence (5). The trial ends when severe or dose-limiting toxicities (DLTs) are experienced by a large fraction of subjects at a given dosage level. The dose just below that which was associated with excessive DLT is defined as the maximum tolerated dose (MTD). In the case of oncology clinical trials, the dose that is the MTD may be recommended for Phase II and Phase III clinical trials. In view of the fact that it may be impossible to predict the toxicity of a newly synthesized chemical, it necessarily follows that many Phase I clinical trials include doses that are too low to be effective against cancers. It has been estimated that about half of subjects treated with the lowest doses receive doses that are "subtherapeutic" (6).

Where subjects are titrated with a drug, it is not the case that any give subject initially receives a lower drug dose, and then receives a higher dose, and then receives an even higher dose. The ICH Guidelines (7) warn against conducting a titration scheme with any one particular subject:

> *A critical disadvantage is that by itself, this study design cannot distinguish response to increased dose from response to increased time on drug therapy or a cumulative drug dosage effect. It is therefore an unsatisfactory design when response is delayed, unless treatment at each dose is prolonged. Even where the time-until-development of effect is known to be short (from other data), this design gives poor information on adverse effects, many of which have time-dependent characteristics.*

In other words, conducting the entire titration scheme with a single human subject cannot distinguish between the drug's effects that are a consequence of only the highest dose (the highest dose in the titration scheme), or if they are a consequence of the cumulative effects of the lowest, intermediate, and highest doses. This source of concern applies to efficacy data and to safety data.

Additional information on arriving at an optimal dose, from the ICH Guidelines, emphasizes the fact that an effective dose and an unacceptably toxic dose may be in a similar or overlapping range, or may reside in well-separated ranges, for any given drug. Facts on whether these ranges are, or are not, well separated can guide the clinician in choosing the starting dose in a Phase I trial (8):

> *For example, a relatively high starting dose (on or near the plateau of the effectiveness dose–response curve) might be recommended for a drug with a large demonstrated separation between its useful and undesirable dose ranges or where a rapidly evolving disease process demands rapid effective intervention. A high starting dose, however, might be a poor choice for*

[5] Koyfman SA, Agrawal M, Garrett-Mayer E, et al. Risks and benefits associated with novel phase 1 oncology trial designs. *Cancer*. 2007;110:1115–1124.

[6] Koyfman SA, Agrawal M, Garrett-Mayer E, et al. Risks and benefits associated with novel phase 1 oncology trial designs. *Cancer*. 2007;110:1115–1124.

[7] ICH Harmonised Tripartite Guideline. Dose–response information to support drug registration E4. March 1994, 12 pages.

[8] ICH Harmonised Tripartite Guideline. Dose–response information to support drug registration E4. March 1994, 12 pages.