**Approved Dose Higher than MTD:**There are several other reasons why the final dose could be higher than MTD including these:

* the patient population is different at Phase 1 to that of the Phase 2-3 (possibly including a new indication), and the safety data show difference in tolerability;
* data could emerge during development suggesting a higher dose (than MTD identified in Phase 1) is required to get efficacy and the available safety data (Phase 1 and later) support it; or
* the approved regimen could be different compared to that tested in Phase 1 (e.g. divided or less frequent dosing).

Four compounds were found to have an approved dose greater than MTD, and were put into the “MTD ≤ approved dose” category. One is aldesleukin with an originally determined MTD of 432 MIU per six-week course, and with an approved dose 1008 MIU per six-week course. Another is doxorubicin hydrochloride with an original MTD determination of 17.5 mg/m2/week and an approved dose of 25 mg/m2/week. The remaining two will be described to help illustrate some of the complexities of this topic.

Vinorelbine tartrate has an MTD of 40 mg/m2 by infusion once every three weeks (1).  It has a maximum approved dose with a different regimen of 30 mg/m2 by infusion every week (2). The total approved dose is thus a total of 90 mg/m2 administered over 3 weeks versus MTD of 40 mg/m2 infused every three weeks.  Administering a lower dose with higher frequency might have improved tolerability which could occur if the maximum concentration (Cmax) is the driver of the AEs which were used to define MTD.  Improved tolerability can also result in higher adherence (fewer drug holidays), which can also improve efficacy in clinical practice.

Irinotecan hydrochloride has an MTD of 320 mg/m2 given by infusion once every three weeks (3), lower than the maximum approved dose of 350 mg/m2 also given by infusion once every three weeks (4).  However, the dosing regimen can be titrated downward to as low as 200 mg/m2 based on the subject’s tolerance.  In this case, there is insufficient information to judge how efficacy could be impacted due to a lower titrated dose.

**References:**

1. [http://rd.springer.com/article/10.1007%2FBF00180813](http://rd.springer.com/article/10.1007%2FBF00180813%20) - Schilling, T., H. Fiebig, et al. (1996). "Clinical phase I and pharmacokinetic trial of vinorelbine administered as single intravenous bolus every 21 days in cancer patients." Investigational New Drugs 14(4): 371-378.
2. <http://www.rxlist.com/navelbine-drug/indications-dosage.htm>
3. [http://www.ncbi.nlm.nih.gov/pubmed/10873073](http://www.ncbi.nlm.nih.gov/pubmed/10873073%20) - Pitot, H. C., R. M. Goldberg, et al. (2000). Phase I Dose-finding and Pharmacokinetic Trial of Irinotecan Hydrochloride (CPT-11) Using a Once-Every-Three-Week Dosing Schedule for Patients with Advanced Solid Tumor Malignancy. 6: 2236-2244.
4. <http://www.rxlist.com/camptosar-inj-drug/indications-dosage.htm>