Supplementary Submission No 16a

INQUIRY INTO OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW

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Dose determination in chemotherapy and immunotherapy

The review of chemotherapy dosing needs to consider the fundamental aspects of this discipline.

1 Clinical response to chemotherapy often ranges from none to complete remission (often temporary). It is therefore difficult to determine the best dose, rather the median value from a clinical trial. This biological variation just says that our knowledge is incomplete and any protocol must be accepted with caution.

2 Dose is often determined in terms of body surface area, a quantity derived from bodyweight. Bodyweight (bwt) is comprised of fat mass (FM) and fat free mass (FFM) compartments. The FFM compartment is comprised of water, protein and bone.

3 Most drugs are water soluble, i.e. they dissolve in water to form a solution. The efficacy of a drug is governed by its concentration. Too low a concentration and the drug is ineffective, too high and its toxic.

4 Dose is usually given in units per kg bodyweight. The higher the bwt, the higher the dose. However, this concept has long been shown to be inadequate in body composition studies, but is still used by Oncologists. Fat is not relevant for a water soluble drug, so ideally the total body water should be used to determine concentration. A more practical approach is that the FFM should be used to determine dose.

5 Let us look at a simple example to prove this point, on the basis that the recommended dose is 1 unit/kg bwt. The "standard man" weighs 70 kg. The dose given would be 70 units. However, for 20% body fat, the FFM would be 70-14 = 56 kg. For a thin person with the same bwt and 10% fat, the FFM = 70-7 = 63 kg. For a fat person with 30% fat, it would be 70-21 = 49 kg.

The drug doses for the **70 kg man with different fat masses** are as follows:

FM%	10	20	30
FFM kg	63	56	49
Dose (relative)	0.89	1.00	1.14

6 Assuming that the average FM% is 20% for the clinical trial dose determination, then the thin man will be under dosed by 11% and the fat man over dosed by 14%.

7 While most patients will lie within this band, very thin and very fat patients will be severely under or over dosed. It is therefore essential that FM be measured first to determine the optimal dose. This is readily done by measuring skin folds with a Vernier caliper. I emphasize that this is not a new concept, but was investigated over 20 years ago.

8 The point of this analysis is that the standard protocol only applies to near standard patients. As such, the Oncology profession itself is guilty of widespread malpractice in dose determination. Even to the extent that an Oncologist who used the correct FFM method could be found guilty of incorrect dosing of patients outside the protocol.

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Note: the author has published 55 papers in the field of In Vivo Body Composition.