



The Trials and Tribulations of the CRM: the DFO Experience

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Outline

- ◆ Overview of Phase I
- ◆ Overview of 3+3 design
- ◆ Overview of CRM
- ◆ the DFO Experience

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Purpose of Phase I

- ◆ To assess safety
- ◆ To find MTD
- ◆ To evaluate PK/PD properties

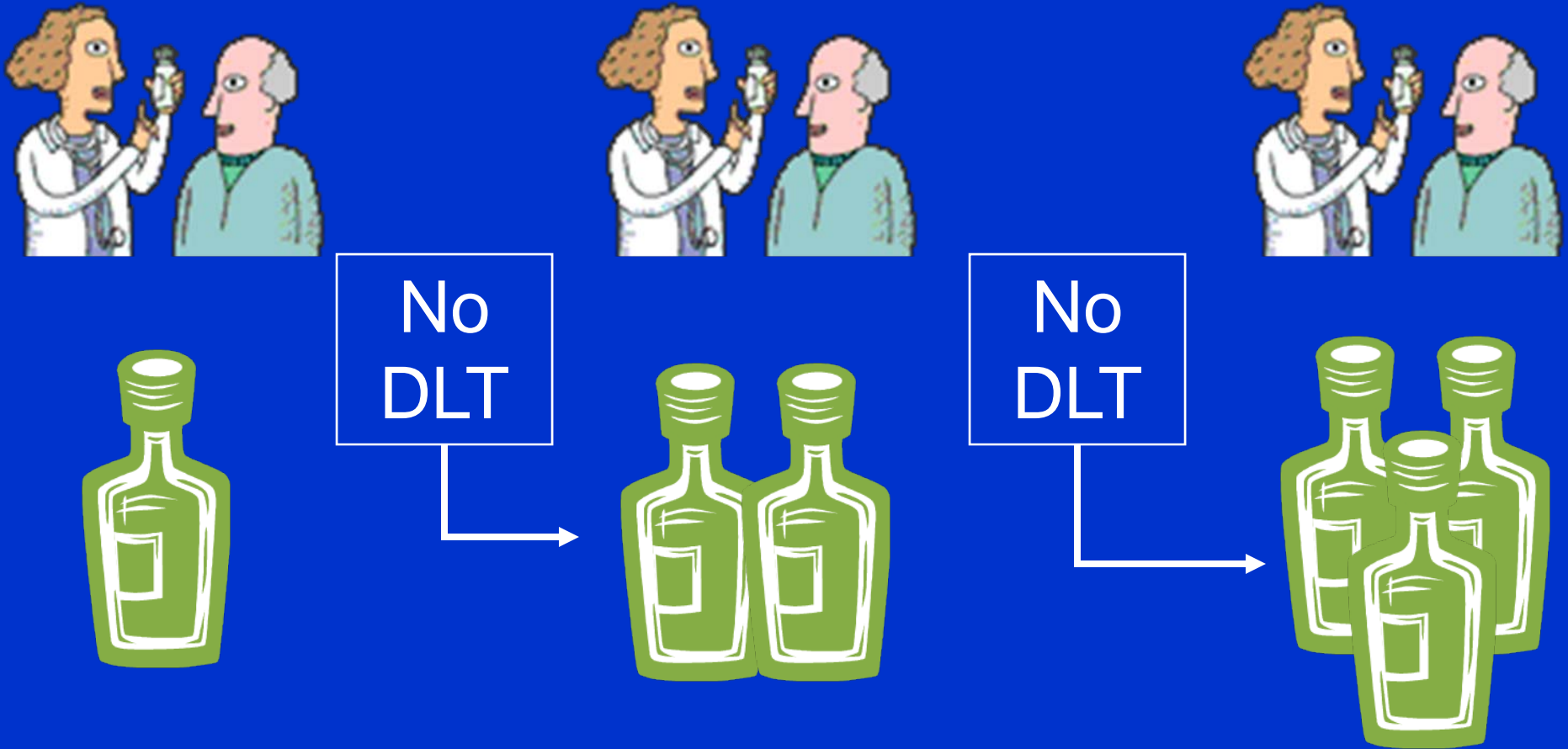
Some Measures of Safety

- ◆ Biological markers (*e.g.*, from serum, urine; blood pressure)
- ◆ Imaging markers
- ◆ Adverse events (*e.g.*, nausea & vomiting, headaches, dizziness; CHF, ICH, death)
- ◆ They define the Dose Limiting Toxicity (DLT)

Premise of Phase I

- ◆ In general, a positive dose-toxic-response relationship exists, *e.g.*, higher the dose, higher the toxicity
- ◆ DLT is *a priori* specified, *e.g.*, various grades of toxicity in cancer (CTCAE v3)
- ◆ Initial dose is known (*e.g.*, from pre-clinical studies)

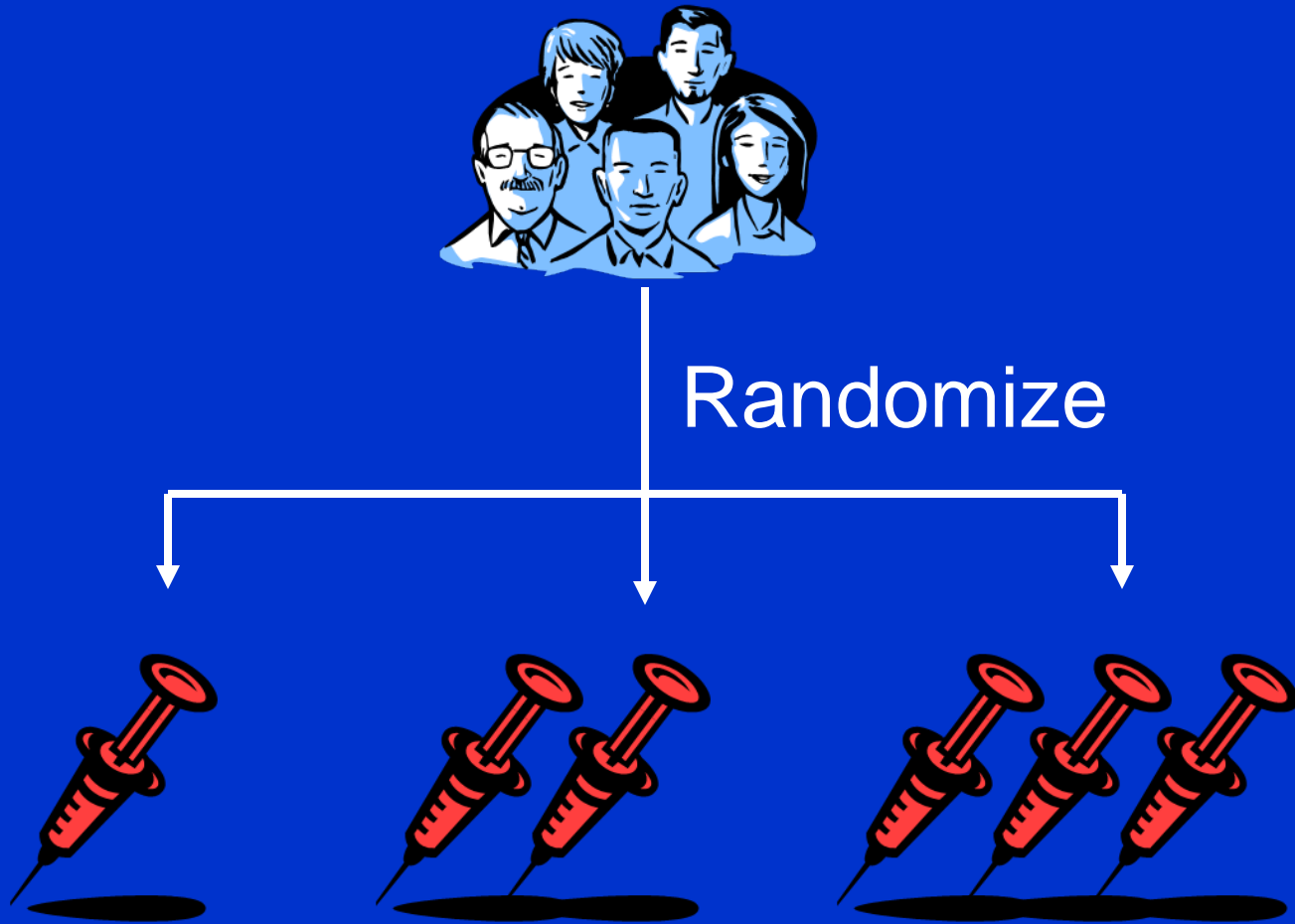
An Ideal Phase I Design



An Ideal Phase I Design

- ◆ Problem – difficult to differentiate the cumulative effects of different doses from the acute effects of the current dose
- ◆ Washout won't solve the problem due to possibly changing conditions of the patient

Another Ideal Phase I Design



Another Ideal Phase I Design

- ◆ Problem - Unethical to give higher doses without first assessing the safety of lower doses

Standard Design

- ◆ “Conventional” / “3+3” / “Up-and-Down”
- ◆ A variety of modified versions are implemented, *e.g.*, only “Up”, different criteria to stop at a dose level
- ◆ All dose levels are fixed and pre-specified

Advantages of Standard Design

- ◆ Easy to set up and relatively simple
- ◆ (Arguable) No need for a statistician to implement

Issues with Standard Design

- ◆ Tend to treat a large number of patients at doses with little potential for efficacy
- ◆ Probability of stopping at an incorrect level may be high
- ◆ Not flexible based on available data

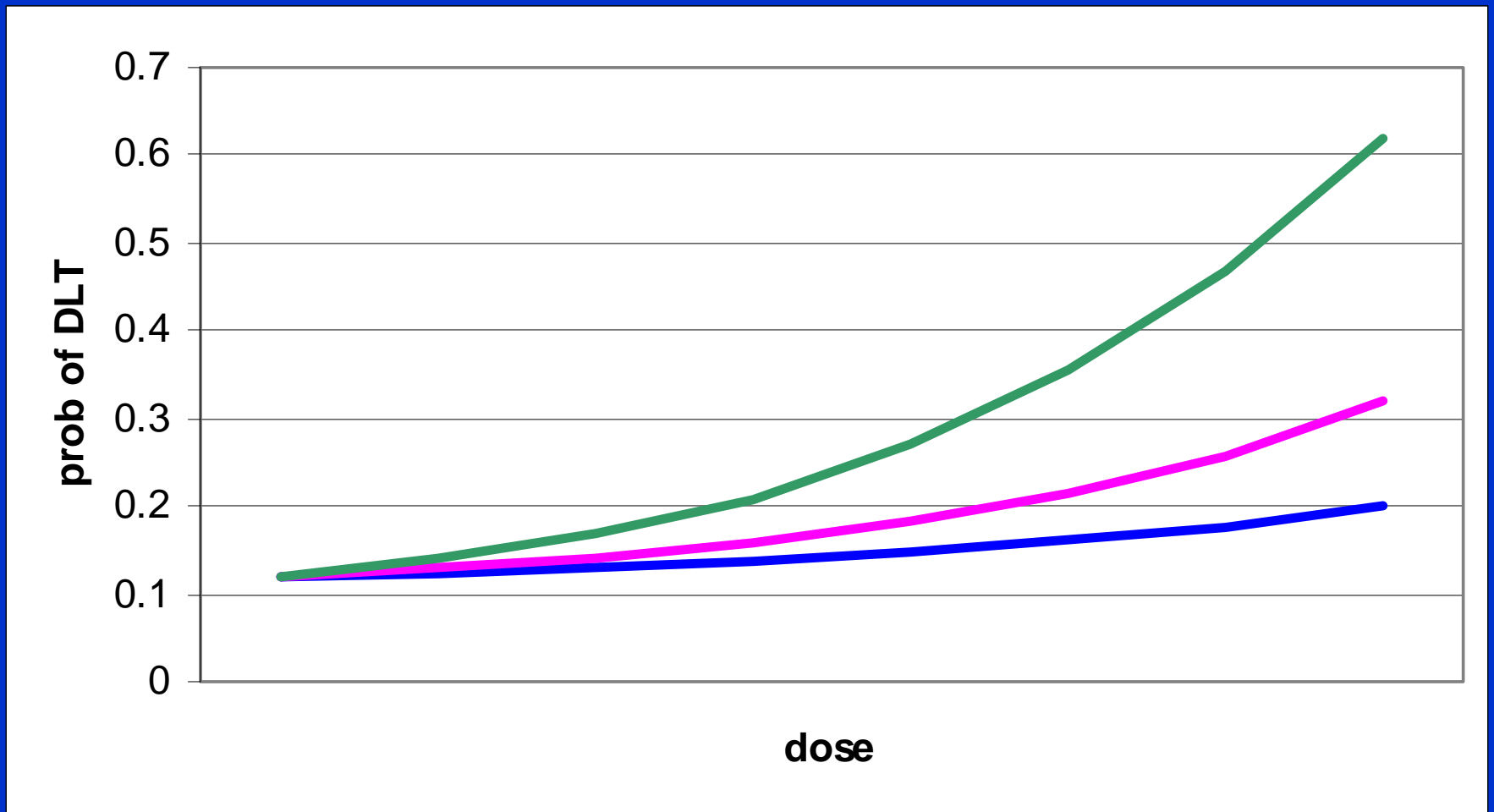
Continuous Reassessment Method (CRM)

- ◆ An adaptive design for Phase I
- ◆ Originally, a Bayesian method to estimate MTD
- ◆ Frequentist versions also available
- ◆ Assumes a one- or two-parameter (θ) math model of a monotonic dose-toxic-response curve

CRM (cont'd)

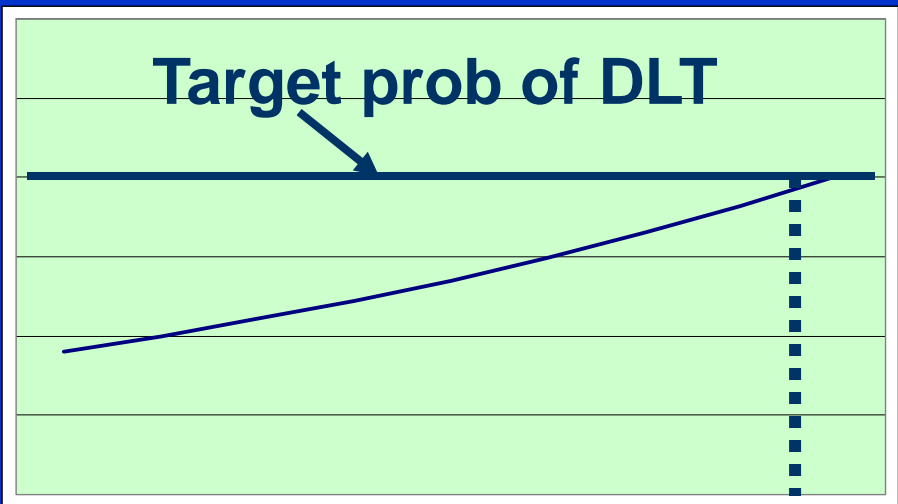
Example 1: $\{1 + \exp[C - (\theta \times \text{dose})]\}^{-1}$

each line has a different value of θ



CRM (cont'd)

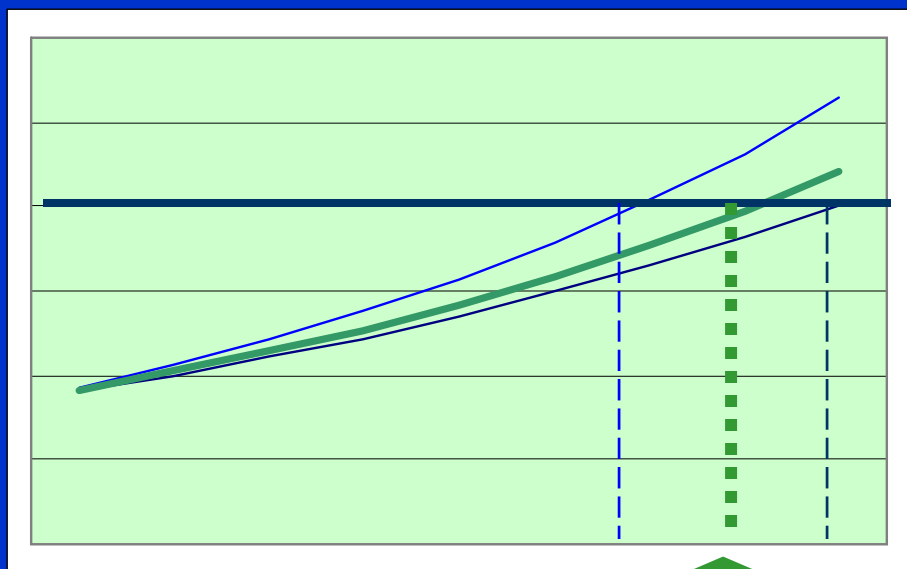
- ◆ Requires prior opinion about θ
- ◆ After new data are acquired, the dose-toxicity-response curve is updated with a new value of θ
- ◆ Then a new dose is selected for the next patient from the updated curve



Pt. 1 - Initial dose



Pt. 2

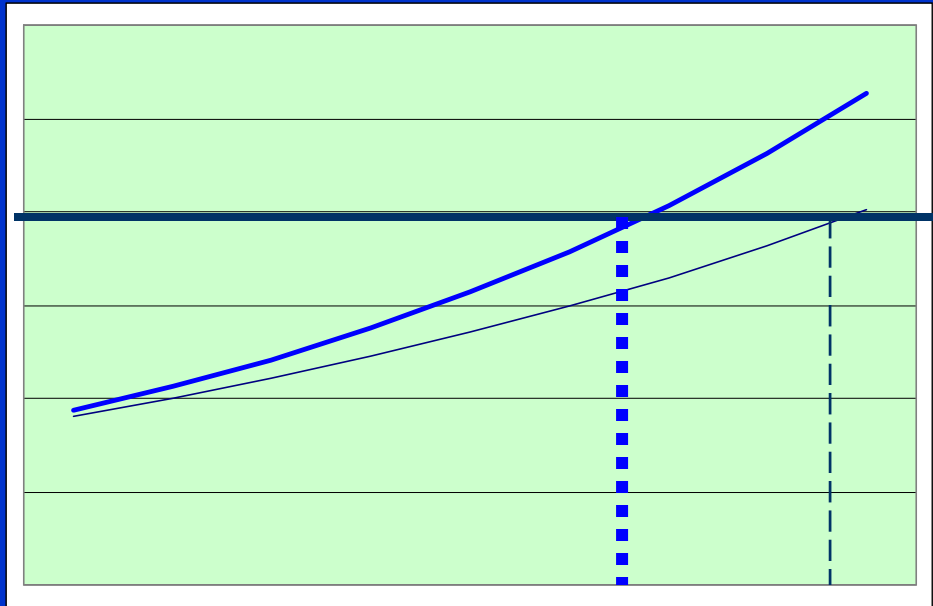


Pt. 4

Hypothetical CRM

X axis=Dose

Y axis=Toxicity



Pt. 3

Advantages of CRM

- ◆ May reach the MTD sooner – more efficient
- ◆ Only need to specify the initial starting dose and the target probability of toxicity
- ◆ Has good statistical properties and not dependent on the initial dose

Issues with CRM

- ◆ Statistician labor-intensive
- ◆ Dependent on the mathematical form of dose-toxic-response model
- ◆ May result in treating a larger proportion of patients at higher doses, especially in early stages of dose-escalation

The DFO Experience

- ◆ Study: deferoxamine (DFO) treatment for spontaneous intracerebral hemorrhage (ICH)
- ◆ Initiate dialogue with the PI in Aug 2006 after out-of-funding-range score of his first NIH R01 submission
- ◆ Primary reason: need statistical input
- ◆ Convince the PI of the CRM design
- ◆ Resubmit in Mar 2007

The DFO Experience (cont'd)

- ◆ Review results: 2.4 percentile
- ◆ Great enthusiasm for CRM by the NIH reviewers
- ◆ In April 2007, FDA clinical reviewers contact the PI questioning the CRM; puts the study on clinical hold
- ◆ The PI requests a statistical review by the FDA upon my urging

The DFO Experience (cont'd)

- ◆ Official clinical hold letter received in Aug 2007!
- ◆ The main issue: need clarification of the CRM, i.e., the FDA clinical reviewers either did not understand or was uncomfortable with CRM

The DFO Experience (cont'd)

“Your dose escalation method and rationale to identify the DLT need to be clearly described in your submission. In addition, since patient safety could be compromised with your current proposed protocol, you should develop a new method with stricter criteria that allows advancement to the next dose. For example, **if one of the three patients experiences a DLT at a certain dose, then that dose could be retested in a new cohort to see if another patient from the new cohort experiences a DLT.**”

The DFO Experience (cont'd)

- ◆ In defense of the FDA, because of the PI's unease, we did include in the CRM, a DSMB review after each cohort *IF* 2 or more of the 3 cohort had DLTs
- ◆ May have been a source of confusion
- ◆ But the FDA clinical reviewers clearly was unfamiliar with the CRM

The DFO Experience (cont'd)

- ◆ Contacted by email one of the prominent biostatisticians at the FDA inquiring about other CRM protocols for IND application
- ◆ The response:

The DFO Experience (cont'd)

“For scientific exchange, there are published articles where CRM in phase I for MTD-finding is used. **Whether it is regulatorily acceptable, though, is a separate question.** In general its merits need to be weighed against its downfalls in the specific disease, drug, patient population under investigation. Hope this gives you some perspectives distinguishing between scientific work and regulatory work.”

The DFO Experience (cont'd)

- ◆ PI submitted the response letter in Aug 2007
- ◆ Talked briefly with Bob O'Neill at the FDA during the FDA-Pharma Workshop in DC in Sep 2007
- ◆ He was not supportive of the hold
- ◆ At the time (may still be), the FDA did not have biostatisticians reviewing Phase I and II clinical trials

The DFO Experience (cont'd)

- ◆ Late Sep 2007, the clinical hold was lifted (by phone) with official letter received in Nov 2007
- ◆ NOA received in Jan 2008
- ◆ Study currently in the 4th dose tier